European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

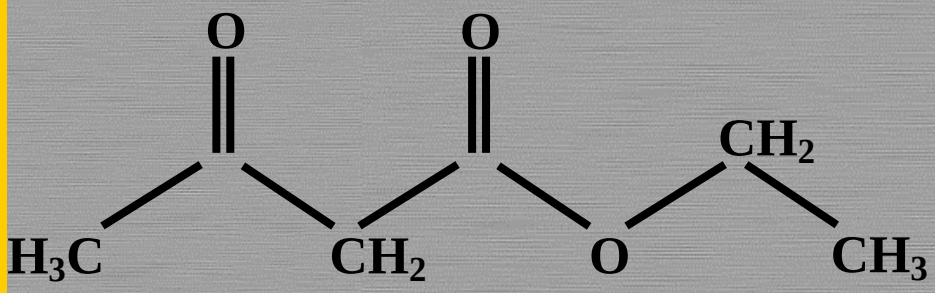
Existing Substances

European Union Risk Assessment Report

CAS No: 141-97-9

EINECS No: 205-516-1

ethyl acetoacetate



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RISK ASSESSMENT

Cataloguing data can be found at the end of this publication

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ETHYL ACETOACETATE

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RISK ASSESSMENT

Final report 2002

Germany

The Rapporteur for ethyl acetoacetate is the Federal Institute for Occupational Safety and Health.

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Review of report by MS Technical Experts finalised:	**March 2001**
Final report:	**2002**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.

The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

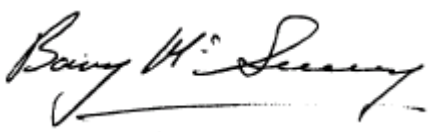
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) which gives its opinion to the European Commission on the quality of the risk assessment.

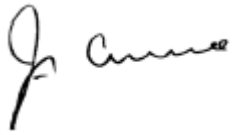
If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.

The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992.

This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.



Barry Mc Sweeney
Director-General
Joint Research Centre



J. Currie
Director-General
Environment, Nuclear Safety and Civil Protection

[1] O.J. No L 084, 05/04/199 p.0001 – 0075

[2] O.J. No L 161, 29/06/1994 p. 0003 – 0011

[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS Number: 141-97-9
EINECS Number: 205-516-1
IUPAC Name: Ethyl acetoacetate

Overall results of the risk assessment

( )	Conclusion (i)	There is need for further information and/or testing.
(X)	Conclusion (ii)	There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.
( )	Conclusion (iii)	There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Summary of conclusions

Environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Human Health (toxicity)

Workers

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Irrespective of conclusion ii for workers for all exposure scenarios and toxicological endpoints information should be given, that occupational exposure levels exceeding those documented in the report cannot be assessed with sufficient certainty.

Consumers

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Human Health (risks from physico-chemical properties)

Given the physico-chemical data, ethyl acetoacetate is considered not to form a risk with respect to flammability, explosive properties, and oxidising properties.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

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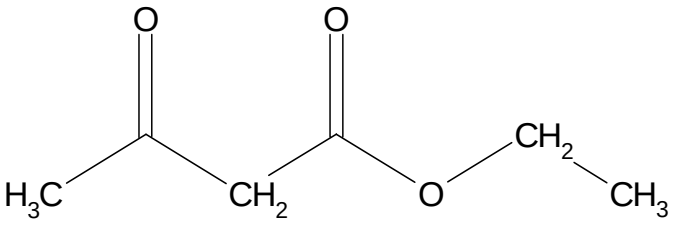
EUSES Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 141-97-9
EINECS Number: 205-516-1
IUPAC Name: Ethyl acetoacetate
Synonyma: 1-Ethoxybutane-1,3-dione
3-Oxobutanoic acid ethylester
Acetessigsäureethylester
Aceto acetato de etilo
Acétoacétate de l'éthyle
Acetoacetic acid, ethyl ester
Butanoic acid, 3-oxo-, ethylester
Butansäure, 3-oxo-, ethylester
Ethylacetoacetat
Ethyl acetoacetate
3-Oxobutansäureethylester
EAA
Ethyl 3-oxobutanoate
Ethyl acetonecarboxylate
Ethyl acetylacetate
Empirical formula: $C_6H_{10}O_3$
Structural formula:



Molecular weight: 130.14 g/mol

1.2 PURITY/IMPURITIES, ADDITIVES

Purity: ≥ 99.0% w/w
Impurity: < 0.5% w/w ethanol
< 0.1% w/w water
<= 0.15% w/w ethyl acetate
<= 0.12% w/w acetone
<= 0.1% w/w methyl acetoacetate
<= 0.1% w/w 3-acetyloxy-2-butenoic acid ethylester
< 0.05% w/w acetic acid
Additives: none

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Summary of physico-chemical properties

Property	Value	Reference
Melting point	-44 - -39°C [1)] - 39°C	Hoechst (1994a) CRC (1991/92)
Boiling point	178 - 187°C	Hoechst (1994a)
Density	1.0325 g/cm^3 at 15°C [2)] 1.0368 g/cm^3 (at 10°C relative to water at 4°C)	Hoechst (1994a) CRC (1991/92)
Vapour pressure	1 hPa at 20°C [3)] 1.3 hPa at 28.5°C	Hoechst (1994a) CRC (1991/92)
Surface tension	62.6 mN/m at 20°C (conc: 1.002 g/l)	Hoechst (1996c) (experimental, Annex V of Directive 92/69/EEC, A.5)
Partition coefficient	logK_{ow} 0.25	Catz & Friend (1989)
Water solubility	125 g/l at 16°C	Hoechst (1994a)
Flash point	65°C	CHEMSAFE
Autoflammability	350°C	CHEMSAFE (experimental according to DIN 51794)
Flammability	not flammable	
Explosive properties	not explosive	structural reasons
Oxidizing properties	not oxidizing	structural reasons
Conversion factors	1 ppm ≅ 5.4 mg/m^3	

[1)] Melting point: in accordance with the literature value, the freezing point given in the safety data sheet was determined to be in the range of -44 and -39 °C.

[2)] Density: The value given in the safety data sheet was confirmed by the literature value.

[3)] Vapour pressure: The value given in the safety data sheet was confirmed by the literature value. The vapour pressure of 1 hPa at 20 °C was used for the calculations in this report.

1.4 CLASSIFICATION

Classification according to Annex I of Directive 67/548/EC: Not classified[4].

In Germany ethyl acetoacetate is classified according to water-hazard class 1 (slightly hazardous to water).

[4] Based on the information available, no classification of the substance is possible, following the criteria set out in Annex VI of Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (OJ B 196, 1.08.1967 p.1).

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

According to information provided in the available IUCLID data sets there are four producers (> 1,000 t/a) of ethyl acetoacetate within the EU. The production volume of each company is between 1,000 and 5,000 t/a. Two of these companies discontinued their production in the territory of the EU in the years 1993 and 1994 respectively. There is no information on possible exports or imports.

The companies produce ethyl acetoacetate wastewater free in closed systems by the addition of ethanol to diketene. The exhaust gases from the production process are drawn off for combustion.

2.2 PROCESSING AND USE

Ethyl acetoacetate is essentially used as an intermediate in the production of pharmaceuticals, plant protection products as well as dyes and pigments. Smaller quantities of the substance are used as fragrance and odour agent. Further possible uses of the substance include employment as a solvent in the paint industry, in cosmetic products such as nail varnish and in the household. It is also described that the substance may be used as a paper impregnating agent and in the coating of paper, as a hardening accelerator for polyester paints, as an additive in the production of resin and in the production of colour films. In aromatic substances identical to those which naturally occur, ethyl acetoacetate may be included in milk products, confectionery, cakes and pastries etc.

According to information provided by the two companies which currently manufacture ethyl acetoacetate, 94.6 % of the substance is used as an intermediate for plant protection products, pharmaceuticals, stabilizers, additives, catalysts and other products. 3.8% are employed as fragrant or odour agent with a wide range of uses (e.g. household chemicals) and 1% is used as a solvent in paints and lacquers. The area of use of the remaining quantity of the substance amounting to 0.6% is not clear.

The use of ethyl acetoacetate in cleaning agents is described in the Danish product register dated January 1995. 9 products with a content of 0 to 1%, 2 products with a content of 1 to 10% and 1 product with a content of 10 to 80% are known. The quantity of the substance used in the 12 products is below 1 t/a.

The substance is listed in the Swedish product register. The information supports the use pattern as it is presented in this report. Ethyl acetoacetate is not included in the Norwegian product register dated 1994.

Table 2.1 shows the main, industrial and use categories and the mass balance of ethyl acetoacetate for the European market.

Table 2.1 Main, industrial and use categories and the mass balance of ethyl acetoacetate for the European market

Main category (MC)	Industrial category (IC)	Use category (UC)	Mass balance [in % of use]
Non-dispersive use (1 b and c)	Chemical industry (3)	Intermediate (33)	94.6
Wide dispersive use (4)	Personal/domestic (5)	Food/feedstuff additive (26) Odour agent (36)	< 0.6 3.8
Wide dispersive use (4)	Pulp, paper and board industry (12)	Coloring agent (10) Impregnation agent (31)	< 0.6 < 0.6
Wide dispersive use (4)	Paint, laquers and varnishes industry (14)	Solvent (48)	1.0

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

3.1.1.1 Release into the environment

Release of ethyl acetoacetate into the environment during production is expected to occur to only a very small extent since production takes place wastewater free and in a closed system and the exhaust gas is drawn off for combustion. Low-level releases into the environment are only expected during cleaning and maintenance work as well as during filling operations. Releases into the wastewater and into the exhaust air are expected during further processing and use of the substance.

No information is available on the remainder content of ethyl acetoacetate in the sequence products.

3.1.1.2 Degradation

Biodegradation

In a recent closed bottle test, 66% degradation was measured after 28 days. After 7 days, 65% ethyl acetoacetate is degraded already and the 10-day window was fulfilled (Hoechst, 1996a). Based on this study the substance can be classified as "readily biodegradable".

From a former respirometric study, only the result of 88% degradation after 5 days is reported (Hoechst 1973). As the study is not well documented there is no information whether industrial or municipal sewage sludge was used as inoculum. Therefore no judgement concerning the ready biodegradability of ethyl acetoacetate can be based on this study.

No results are available from simulation tests on biodegradation in wastewater treatment plants (WWTPs), in the aquatic compartment and in soil. Consequently, taking into account the above-mentioned investigation, in accordance with the Technical Guidance Document (TGD) the following degradation constants can be deduced:

Table 3.1 Degradation constants

Compartment	Degradation constant
WWTP	$k_{WWTP} = 1\ h^{-1}$
Surface water	$k_{SW} = 4.7 \times 10^{-2}\ d^{-1}$
Sediment	$k_{SED} = 0.002\ d^{-1}$
Soil	$k_{SOIL} = 0.023\ d^{-1}$

(for calculation see Appendix 1)

Photodegradation

Direct photolysis of ethyl acetoacetate in the atmosphere is not to be expected. However, gaseous ethyl acetoacetate reacts in the atmosphere with hydroxyl radicals which have been formed photochemically. Based on an atmospheric concentration of the OH-radicals of $5 \cdot 10^5$ OH/cm^3 and the rate constant ($kdeg_{air}$) of $1.55 \cdot 10^{-12}$ cm^3 molecule^{-1} s^{-1}, the calculated half-life for photochemical degradation in the atmosphere amounts to 10.3 days (Hoechst AG 1994b).

Hydrolysis

Ethyl acetoacetate is in principle hydrolysable. However, no investigations are available in this regard. Half-lives for hydrolysis amounting to between approx. 15 days (pH = 8) and 149 days (pH = 7) were calculated for the substance with the aid of QSAR calculations. The half-lives calculated via QSAR cannot be included quantitatively in the assessment. However, they permit the conclusion that hydrolysis is not a significant elimination process with regard to ethyl acetoacetate in the environment (for calculation see Appendix 1).

3.1.1.3 Distribution

A Henry constant of 0.104 Pa m^3/mol is calculated on the basis of the data relating to the vapour pressure and solubility of ethyl acetoacetate which are provided in Chapter 1. Accordingly, as an aqueous solution, the substance is moderately volatile (for calculation see Appendix 1).

No bioaccumulation potential is to be expected due to the measured $logP_{ow}$ value for ethyl acetoacetate of 0.25. On the basis of this value, following the TGD, the Koc-value is calculated as 14.125 l/kg and the partition coefficients can be calculated according to the organic carbon content in the individual environmental compartments (see **Table 3.2**).

Table 3.2 Partition coefficients

Compartment	Partition coefficient
Soil-water	$K_{p\text{-}soil}$ = 0.283 l/kg
Sediment-water	$K_{p\text{-}sed}$ = 0.706 l/kg
Suspended matter-water	$K_{p\text{-}susp}$ = 1.413 l/kg
Sewage sludge-water	$K_{p\text{-}sludge}$ = 5.226 l/kg

(for calculation see Appendix 1)

Using the distribution model according to Mackay (level 1), the following theoretical distribution in the environment results for ethyl acetoacetate:

Table 3.3 Theoretical distribution in the environment

Compartment	Percentage
Atmosphere	3.5
Hydrosphere	96.0
Soil	0.25
Sediment	0.25

Consequently, the hydrosphere is the target compartment for ethyl acetoacetate in the environment.

Elimination in WWTPs

Based on the physico-chemical properties of ethyl acetoacetate and taking into account the degradation rate for biodegradation of 1 h^{-1}, the elimination in WWTPs (as a result of biodegradation and distribution processes) can be determined using the Simple Treat model in accordance with the TGD as follows:

Table 3.4 Elimination in WWTPs

Evaporation to air (%)	0
Release (dissolved) to water (%)	12.6
Adsorpion to sewage sludge (%)	0
Degradation (%)	87.4
Total elimination from water (%)	87.4

3.1.1.4 Accumulation

No investigations on bioaccumulation are available. The measured $logP_{ow}$ of 0.25 does not indicate any relevant bioaccumulation potential. In accordance with the TGD a BCF for fish of 0.325 l/kg is calculated (for calculation see Appendix 2).

Likewise the calculated Koc-value of 14.125 l/kg does not indicate either that a significant geoaccumulation potential is to be expected for ethyl acetoacetate. Consequently, the substance can be washed out of the soil into the ground water by rain water depending on the elimination in soil by degradation and distribution.

3.1.2 Aquatic compartment

The actual production volumes provided by the companies are taken into account as the basis for calculating the $Clocal_{water}$. However, since the actual production volumes may change within the indicated ranges given in the IUCLID database, in a generic (non site-specific) approach the $Clocal_{water}$ for production and further processing is calculated on the basis of the highest single production quantity.

Releases into the aquatic compartment do not occur during production since all of the manufacturers produce the substance wastewater free in a closed system. Since no exposure data has been submitted with regard to further processing, in accordance with the ESD for intermediates (Emission Scenario Documents; IC - 3), release into the wastewater amounting to 0.7% of the processing quantity is expected.

3.1.2.1 Determination of Clocal $_{water}$ / Generic approach: production and processing

A generic exposure scenario for the release of intermediates into the wastewater during production and further processing is described in the TGD. This corresponds to a realistic "worst-case" scenario. Taking into account the wastewater free production amounting to max. 5,000 t/a and simultaneous processing of this amount at one site, a $Clocal_{water}$ amounting to approx. 2.84 µg/l is calculated for production and further processing.

3.1.2.2 Determination of Clocal $_{water}$ / Site-specific approach: production and processing

A Clocal $_{water}$ calculation for the sites can be undertaken using the currently available information on the individual manufacturers. For company A, a $Clocal_{water}$ of 1.45 µg/l results and for company B a $Clocal_{water}$ of 1.47 µg/l. On the pre-condition that approx. 1,000 t/a of the substance are processed at an unknown place, a $Clocal_{water}$ of 1.70 µg/l results.

Table 3.5 Determination of $Clocal_{water}$ / Site-specific approach - production and processing

Site	Release to waste water (kg/d)	Size of STP * (m^3/d)	Min. flow of receiv. Water (m^3/s)	Conc. effluent STP (µg/l)	Conc. receiv. water (µg/l)
A	69.9 [1)]	70800	70.5	124.4	1.45
B	30.3	20700	30	185.5	1.47
C	70 [1)]	[2)]	60 [1)]	[2)]	1.70

[1)] based on the default value of the TGD
[2)] based on the ESD - IC 3 volumes of waste water flow are not taken into account
* STP: sewage treatment plant

3.1.2.3 Determination of the Clocal $_{water}$ for the use of Ethyl acetoacetate

For those application areas where no emission scenario document is available or the existing emission scenario document is not applicable because some underlying information is missing (odour agent in household chemicals and solvent in paints and lacquers) for ethyl acetoacetate the A- and B- tables of Appendix I of the TGD are used to derive the emission factors. In accordance with the TGD as a reasonable worst-case approach the fraction of main source was determined on the basis of the total amounts of ethyl acetoacetate used within the EU in the respective application area.

In the case of use as an odour agent in household chemicals it is assumed that the entire quantity which is used enters the household wastewater or that a part enters the atmosphere as a result of volatilization. It is assumed in the exposure consideration that 3.8 % of the production quantity is used in this area. The exposures are to be expected both during the formulation and use of household chemicals.

During use of ethyl acetoacetate as a solvent in paints and lacquers, exposures are to be expected both during the formulation and processing of the paints and lacquers. 1% of the production quantity is currently used in this area.

It is not necessary for a $Clocal_{water}$ to be estimated for use of the substance in paints and lacquers employed by the public at large on account of the small quantity which is involved and the diffuse distribution.

In addition to use as an odour agent in household chemicals and as a solvent in the paint and lacquer industry, the use of ethyl acetoacetate in paper coating and paper impregnation is also described in the literature. No information is available on the current relevance of this use of the substance. For assessment purposes it is assumed that the quantity of the substance whose use is currently not clear, amounting to 0.6% of the production quantity, is employed in the area of paper coating. As a result of use of the substance in paper coating or paper impregnation, the substance enters the wastewater of the relevant companies during paper recycling.

Table 3.6 summarizes the results of the calculations of $Clocal_{water}$ performed according to the TGD.

Table 3.6 Determination of the $Clocal_{water}$ for the use of ethyl acetoacetate

Types of use	Household chemicals	Household chemicals	Solvent in paints and lacquers	Paper coating and paper impregnation
Tonnage	3.8 % of the prod. quantity	3.8 % of the prod. quantity	1 % of the prod. quantity	0.6 % of the prod. quantity
Main category	non-dispersive use (Ic)	wide dispersive use	non-dispersive use (Ic)	non-dispersive use
Industrial category Use category	5 (personal/domestic) 36 (odour agents)	5 (personal/domestic) 36 (odour agents)	14 (paints) 48 (solvent)	12 (paper and boards) 10 (coloring agents) 31 (impregnation agents)
Life cycle step	formulation	private use	formulation	paper recycling
Number of days	64 (B-table 2.1)	365 (B-table 4.1)	54 (B-table 2.1)	250 (IC - 12)
Release factor to water	0.02 (A-table 2.1)	0.8 (A-table 4.1)	0.2 (A-table 2.1)	0.09 (based on IC - 12)
Fraction of main source	0.6 (B-table 2.1)	0.002 (B-table 4.1)	1 (B-table 2.1)	-
Size of STP (m^3/d)	2,000	2,000	2,000	2,000
Dilution in receiv. water	10	10	10	10
$Clocal_{effl.}$ (µg/l)	1,264	29.55	630	39
$Clocal_{water}$ (µg/l)	126	2.95	63	3.9

3.1.2.4 Data relating to occurrence in the hydrosphere

No measured values are available for the occurrence of ethyl acetoacetate in the hydrosphere.

3.1.2.5 Sediment

No data are available for ethyl acetoacetate, neither with regard to its occurrence in sediment nor to its effect on benthic organisms. On the basis of the known physico-chemical properties there is no indication of ethyl acetoacetate accumulating in sediment.

3.1.3 Atmosphere

Release into the atmosphere during production of ethyl acetoacetate at company A is given as 29 kg/a. No further information with regard to release into the atmosphere during production and processing or use of the substance is available. No releases of the substance into the atmosphere are to be expected during paper recycling. An estimation of a $Clocal_{air}$ is not necessary with regard to the use of the substance in paints and lacquers by the public at large on account of the small quantity which is used and the diffuse distribution.

Taking into account the exposure tables in Annex 1 of the TGD, the releases into the atmosphere and the resultant deposition quantities can be calculated on the basis of the physico-chemical properties of the substance and the quantities of the substance involved in production, processing and use.

Table 3.7 summarizes the results of the calculations of $Clocal_{air}$ and $DEPtotal_{ann.}$ performed according to the TGD.

Table 3.7 Results of the calculations of $Clocal_{air}$ and $DEPtotal_{ann}$

Company/Types of use	Site A	Site B	Site C	Household chemicals	Household chemicals	Solvent in paints and lacquers
Tonnage	-[1)]	-[1)]	1,000 t/y	3.8 % of the prod. quantity	3.8 % of the prod. quantity	1 % of the prod. quantity
Main category	Ib	Ib	Ic	non-dispersive use (Ic)	wide dispersive use	non-dispersive use (Ic)
Industrial category Use category	3 33	3 33	3 33	5 (personal/domestic) 36 (odour agents)	5 (personal/domestic) 36 (odour agents)	14 (paints) 48 (solvent)
Life cycle step	prod. / proc.	prod. / proc.	proc.	formulation	private use	formulation
Number of days	300 / 136 (B-table 1.6 / 3.2)	300 / 33 (B-table 1.6 / 3.2)	100 (B-table 3.2)	64 (B-table 2.1)	365 (B-table 4.1)	54 (B-table 2.1)
Release factor to air *sites specific data	0.0000207* / 0.00001 (A-table 3.3)	0.0001 (A-table 1.2) / 0.00001 (A-table 3.3)	0.0001 (A-table 3.3)	0.005 (A-table 2.1)	0.2 (A-table 4.1)	0.005 (A-table 2.1)
Fraction of main source	1	1	1	0.6 (B-table 2.1)	0.002 (B-table 4.1)	1 (B-table 2.1)
Emission to air from STP in %	0	0	0	0	0	0
$Clocal_{air}$ (mg/m^3)	$5.46 \cdot 10^{-5}$	$1.34 \cdot 10^{-4}$	2.78 · 10-4	$1.39 \cdot 10^{-3}$	$3.26 \cdot 10^{-5}$	$6.95 \cdot 10^{-4}$
$DEPtotal_{ann.}$ ($mg/m^2 \cdot d$)	$4.66 \cdot 10^{-5}$	$1.54 \cdot 10^{-4}$	1.1 · 10-4	$3.52 \cdot 10^{-4}$	$4.7 \cdot 10^{-5}$	$1.48 \cdot 10^{-4}$

[1)] confidential information

3.1.4 Terrestrial compartment

Release of ethyl acetoacetate to soil as a result of deposition from the atmosphere is to be expected. The point source of production and further processing as well as the use of the substance involving the highest contamination of the air are considered here (see Section 3.1.3).

The following table summarizes the results of the above-mentioned exposure scenarios for release of the substance to soil.

Table 3.8 Release of ethyl acetoacetate to soil as a result of deposition from the atmosphere

Type of use	Route of exposure	Clocal $_{soil\ porewater}$ in mg/l	Clocal $_{soil}$ in mg/kg
Production and further processing of the substance at company B	deposition	4.50 · 10-5	1.65 · 10-5
Formulation of household chemicals	deposition	1.03 · 10-4	3.78 · 10-5
Formulation of paints and lacquers	deposition	4.33 · 10-5	1.59 · 10-5

Based on the SimpleTreat model (see Section 3.1.1) there is no adsorption of ethyl acetoacetate at sewage sludge to be expected and the release to soil with sewage sludge application in agriculture is not taken into account in the risk assessment.

3.1.5 Non compartment specific exposure relevant to the food chain

Since there is no indication of ethyl acetoacetate having a bioaccumulation potential, it is not necessary to undertake a risk characterization for exposure via the food chain. In aromatic substances identical to those which naturally occur, ethyl acetoacetate may be included in milk products, confectionery, cakes and pastries etc.

3.1.6 Regional exposure consideration

All releases, from both point sources and diffuse sources, are considered in the determination of a regional background concentration. The releases of ethyl acetoacetate from point sources of the production and processing sites are small in the relation to the emission from the use of the substance. Due to this situation the following approach was chosen: the total emission quantity is considered in the continental model and 10% of it in the defined regional EU standard model (densely populated area of 200 · 200 km with 20 million inhabitants).

3.1.6.1 Release into the hydrosphere and the atmosphere during production and processing

Based on the current exposure estimation from the Sections 3.1.3.2 and 3.1.4, the exposure quantities for release into the hydrosphere and the atmosphere are summarized in **Table 3.9**. In the case of release into the hydrosphere, the elimination in the industrial WWTPs has already been taken into consideration.

Table 3.9 Release into the hydrosphere and the atmosphere during production and processing

Company	Release into the hydrosphere in t/a	Release into the atmosphere in kg/a
Company A	1.2	42.6
Company B	0.13	140.5
No information	0.88	100
Total	2.21 t/a	283.1 kg/a

3.1.6.2 Point sources for release into the soil

No direct release into the soil was identified. Diffuse release into the soil only occurs as a result of distribution processes. Release is therefore to be expected as a result of deposition from the air (see Section 3.1.4).

3.1.6.3 Exposure sources arising from use

Diffuse releases into the hydrosphere and atmosphere are to be expected during the use of ethyl acetoacetate as an odour agent in household chemicals and during the use of paints and lacquers by the public at large. Taking into consideration the use of the substance as an odour agent in household chemicals and the exposure scenarios provided in Annex 1 of the TGD, it is estimated that 20 % is released into the atmosphere. The remainder enters the wastewater. On account of the small quantity used and the diffuse distribution, a $Clocal_{water}$ is not calculated for ethyl acetoacetate which is contained in paints and lacquers used by the public at large. However, for the regional exposure consideration it is assumed that the total quantity which is used is released into the atmosphere.

Since not all of the diffuse releases resulting from use of the substance enter the hydrosphere directly but, instead, mainly enter the wastewater which is possibly cleaned in municipal WWTPs, the calculation for these scenarios is based on an 70 % connection to WWTPs in which biodegradation of 87.4 % of the substance occurs. The remaining 30 % of the wastewater is discharged directly into the hydrosphere.

Point-source releases (see Sections 3.1.2.3 and 3.1.3) which require consideration result from the use of ethyl acetoacetate as a solvent and as a paper auxiliary.

Table 3.10 summarizes the individual environmental releases.

Table 3.10 Individual environmental releases

Area of use	release into the hydrosphere in t/a		release into the atmosphere in t/a
	direct	via WWTPs	
Formulation of household chemicals	/	0.27	0.535
Odour agent in household chemicals	25.7	7.5	21.4
Formulation of paints and lacquers	/	0.07	0.135
Use of paints and lacquers by the public at large	/	/	27
Paper recycling	/	0.19	/
total	25.7	8.0	49.07

The individual releases for the calculation of the continental and regional models are summarized in **Table 3.11**.

Table 3.11 Individual releases for the calculation of the continental and regional models

Release to		Continental model in t/y	Regional model in t/y
air - direct		49.4	5
soil - direct		no direct releases	no direct releases
water	- direct	25.7	2.6
	- via WWTPs	10.2	1

The input data for the model calculations are presented in greater detail on the website (http://ecb.jrc.it). The following regional environmental concentrations result from the calculations.

$PECregional_{aquatic}$ = 0.04 µg/l
$PECregional_{air}$ = 0.37 ng/m^3
$PECregional_{agr.soil}$ = 1.8 ng/kg
$PECregional_{natural\ soil}$ = 3.5 ng/kg

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT) ASSESSMENT

3.2.1 Aquatic compartment

3.2.1.1 Determination of the $PNEC_{aqua}$

Only a few valid data on ecotoxicological effects of ethyl acetoacetate exist, which are listed in **Table 3.12.**

Table 3.12 Ecotoxicological effect data of ethyl acetoacetate

Species	Effect concentration	Reference
Leuciscus idus	48h LC_{50} = 275 mg/l 48h LC_{50} = 515 mg/l	Juhnke, Lüdemann 1978
Daphnia magna	24h EC_{50} = 790 mg/l	Bringmann, Kühn 1977
Daphnia magna	24h EC_{50} = 800 mg/l	Bringmann, Kühn 1982
Scenedesmus subspicatus	72h EC_{50} > 500 mg/l 72h EC_{10} > 500 mg/l	Hoechst 1996b
Scenedesmus quadricauda	8d EC_3 = 7.6 mg/l	Bringmann, Kühn 1978, 1980a
Microcystis aeruginosa	8d EC_3 = 90 mg/l	Bringmann, Kühn 1976, 1978

Long-term toxicity tests with fish and invertebrates are not available.

If ethyl acetoacetate is regarded as a non-polar narcotic substance, QSAR estimations can be performed using the equations for non-polar narcotics given in Chapter 4 of the TGD.

Table 3.13 QSAR estimations using the equations for non-polar narcotics.

Species	Endpoint	Value
Pimephales promelas	96h-LC_{50}	3250 mg/l
Brachydanio rerio/Pimephales promelas	28 - 32d-NOEC	388 mg/l
Daphnia magna	48h-EC_{50}	3600 mg/l
Daphnia magna	16d-NOEC	1000 mg/l
Selenastrum capricornutum	72 - 96h-EC_{50}	4300 mg/l

The only reliable study with fish was conducted over a 48-hour period with *Leuciscus idus* (Juhnke, Lüdemann 1978). The aim of this study was to prove reproducibility of the results obtained with the standard test method DIN 38 412 L 15 from different laboratories. Fish were exposed in a static system for 48 h. Apart from the shorter exposure time the method is comparable to the OECD Guideline 203. 48 h-EC50-values of 275 mg/l respectively 515 mg/l were found. The corresponding LC100-values were 306 and 597 mg/l. The test media were neutralized.

Two different acute tests with *Daphnia magna* resulted in almost equal EC50-values of 790 and 800 mg/l ethyl acetoacetate after 24 hours with respect to immobility (Bringmann, Kühn 1977, 1982). As it could be observed with fish the LC100-values for *Daphnia* were in the same range with the EC50-values that are 1,250 and 1,136 mg/l. The pH-values were adjusted between 7.6 and 8.

In a recent study with *Scenedesmus subspicatus* conducted according to EU/OECD guideline and with GLP no effects on growth rate or biomass could be observed after 72 hours at a concentration of 500 mg/l (Hoechst, 1996b). Lower toxic threshold concentrations (EC3-values) were determined for *Scenedesmus quadricauda* as 7.6 mg/l and *Microcystis aeruginosa* as 90 mg/l (Bringmann, Kühn 1976, 1978, 1980a). A possible explanation of the different results may be that in the latter test the algae had not been in the exponential growth phase during the whole test duration of 8 days. Therefore it should be a case-by-case decision if the 8-d growth inhibition test by Bringmann/Kühn has to be considered for the risk assessment. As for ethyl acetoacetate a more recent algae study according to EU/OECD guideline with GLP is available this study should be regarded as more relevant for the assessment.

There was no analytical monitoring in almost all of these tests, but DOC measurements in the algae test of Hoechst 1996b showed no disappearance of ethyl acetoacetate in 72 hours. As this has to be expected for the other tests as well and the pH-values were adjusted in a neutral range the ecotoxicological results can be rated as valid.

The experimental data indicate that fish might be slightly more sensitive to ethyl acetoacetate than daphnia or algae. This is also confirmed by the QSAR estimations.

As only acute studies for the aquatic compartment are available an assessment factor of 1,000 is applied.

Therefore: $PNEC_{aqua}$ = 275 mg/l /1,000 = 275 µg/l

3.2.1.2 Determination of the $PNEC_{microorganisms}$

For the derivation of the $PNEC_{microorganisms}$ the following data from non-standard tests with protozoa and bacteria are relevant. These are nominal values and the test media were neutralized.

Table 3.14 Data used for the derivation of the $PNEC_{microorganisms}$

Species	Effect concentration	Reference
Chilomonas paramaecium	48h EC_5 = 435 mg/l	Bringmann et al. 1980b
Entosiphon sulcatum	72h EC_5 = 391 mg/l	Bringmann, Kühn 1980a
Uronema parduczi	20h EC_5 = 596 mg/l	Bringmann, Kühn 1980c
Pseudomonas putida	16 h EC_3 = 33 mg/l	Bringmann, Kühn 1976, 1980a

The toxic threshold concentrations (EC5-values) for different species of protozoa were derived in cell multiplication inhibition tests showing less sensitivity than for *Pseudomonas putida*, which was assessed in a cell multiplication inhibition test as well.

According to the TGD, *Pseudomonas* test must be numbered among the more sensitive tests and an assessment factor of 1 has to be applied. Accordingly, the following value results:

$$PNEC_{microorganisms} = 33 \text{ mg/l} / 1 = 33 \text{ mg/l}$$

3.2.1.3 Sediment

Neither measured concentrations of ethyl acetoacetate for sediments nor experimental studies with sediment organisms are available. There are no indications of adsorption of the substance to sediments, no risk assessment is required for this compartment.

3.2.2 Atmosphere

No ecotoxicological data are available for this environmental compartment. Abiotic effects are not to be expected on account of the short half-life.

3.2.3 Terrestrial compartment

No ecotoxicological data are available for terrestrial organisms. In approximation, the aquatic PNEC can be used for the purpose of risk assessment with regard to the terrestrial compartment and be compared with the concentration determined for the soil pore water.

$$PNEC_{soil} = 275 \text{ µg/l (soil pore water)}$$

3.2.4 Non compartment specific effects relevant to the food chain

Since ethyl acetoacetate does not reveal a bioaccumulation potential, it is not necessary for a corresponding PNEC to be derived.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment

3.3.1.1 WWTP

The highest effluent concentration for a WWTP was calculated for use in the formulation of household chemicals. It amounts to 1.264 mg/l. A generic model for the calculation of the $Clocal_{eff}$ is involved here. No specific information on exposure to the environment is available. Consequently, in accordance with the TGD, standard scenarios had to be used in the calculation of the $Clocal_{eff}$. Taking into account the $PNEC_{microorganisms}$ of 33 mg/l, a $Clocal_{eff}$/PNEC ratio of 0.04 results. Since the $Clocal_{eff}$/PNEC ratio is < 1, there is no risk to the microorganism population of the WWTP.

3.3.1.2 Aquatic environment

Table 3.15 summarizes the PEC/PNEC ratios for all areas of production, processing and use (PEC = $Clocal_{water}$ + $Cregional_{aquatic}$):

Table 3.15 PEC/PNEC ratios for all areas of production, processing and use

Company / area of use	PEC = $Clocal_{water}$ + $Cregional_{aquatic}$ in µg/l	PEC/PNEC
Production and/or processing:		
• maximum production and processing	2.84 + 0.04 = 2.88	0.01
• amounting to 5,000 t/a (generic approach)		
• company A	1.45 + 0.04 = 1.49	0.005
• company B	1.47 + 0.04 = 1.51	0.005
• unknown site1000 t/a processing	1.70 +0.04 = 1.74	0.006
Odour agent in household chemicals	2.96 + 0.04 = 3.0	0.011
Formulation of household chemicals; substance as a odour agent	126.4 + 0.04 = 126.44	0.46
Formulation of paints and lacquers; substance as a solvent	63 +0.04 = 63.04	0.23
Paper recycling / substance as a component in paper coating and impregnation	3.9 + 0.04 = 3.94	0.014

With regard to the areas of use with a PEC/PNEC ratio < 1, on the basis of the currently available data there is no risk to aquatic organisms.

3.3.1.3 Sediment

No data are available for ethyl acetoacetate in connection with its occurrence in sediment. Neither are there any studies on its effect on benthic organisms. According to the physico-chemical properties which are currently known, there is nothing to indicate that ethyl aceto-acetate accumulates in sediment. Therefore a risk assessment is not necessary for this compartment.

3.3.2 Atmosphere

On account of the atmospheric half-life ($t_{½}$ = 10.3 days), abiotic effects on the atmosphere, such as global warming and ozone depletion, are not to be expected in connection with ethyl acetoacetate.

The highest calculated concentration for the air amounts to 1.4 µg/m^3 and relates to the formulation of household chemicals. Since no data are available with regard to the ecotoxicological effect of the substance on this environmental compartment, it is not possible to undertake a quantitative assessment for this environmental compartment. On the basis of the information which is available on the substance, the performance of tests is not considered necessary.

3.3.3 Terrestrial compartment

Releases into the terrestrial compartment are to be expected as a result of deposition from the atmosphere. The highest deposition rate results from the calculations relating to the use of the substance in the formulation of household chemicals. This results in soil concentrations for ethyl acetoacetate of 37.8 ng/kg (wet soil) or 0.103 µg/l soil pore water.

Since no ecotoxicological data are available for terrestrial organisms, in approximation, the aquatic PNEC is referred to a risk assessment for the terrestrial compartment and is compared with the concentration determined for the soil pore water. The PEC/PNEC ratio of 0.0003 is clearly under 1 and there is currently no indication of a risk to the terrestrial environmental compartment.

3.3.4 Non compartment specific effects relevant to the food chain

Since there is no indication of a bioaccumulation potential of ethyl acetoacetate, risk characterization in connection with exposure via the food chain is not required. In aromatic substances identical to those which naturally occur, ethyl acetoacetate may be included in milk products, confectionery, cakes and pastries etc.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

Ethyl acetoacetate is primarily used as a chemical intermediate for the manufacture of pharmaceuticals, pesticides, dyes and pigments.

Apart from these uses, approximately 5 % of the total produced quantity is employed:

- directly or in perfume oils (in concentrations up to 5 %) as fragrance or odorant (for e.g. body care products, detergents and sanitary cleaning products, room deodorants),
- as a flavouring substance in foodstuffs,
- as a solvent for cosmetics (particular for nail varnish),
- as an additive in resin manufacture,
- as a hardening accelerator in polyester paints (1%, see Section 2.2),
- for impregnating and coating of paper,
- in the manufacture of colour films (see Section 2.2).

4.1.1.2 Occupational exposure

Occupational exposure limits for ethyl acetoacetate are not known.

4.1.1.2.1 Occupational exposure during production and further processing in the chemical industry

Production and further processing as a chemical intermediate

The production and further processing as a chemical intermediate generally takes place continuously in closed systems. According to information provided by two producers, within the company the substance is transported via closed pipes and is stored in tanks. Gas exchange is employed for example during the filling of tank wagons, and local exhaust ventilation is employed during the filling of drums. Exposure associated with transporting the chemical would result from coupling and uncoupling transfer lines and drumming operations. The containment (e.g. columns for distillation, tanks) is breached for sampling for approx. 2 minutes. In case of the columns several times per day samples are taken and analysed.

The results of two workplace measurements provided by one company (personal and stationary, 8h-TWA (time weighted average)) in the production plant and in the tank wagon / dispatch area were less than 10 % of the company´s internal limit (185 ml/m³ = 1,000 mg/m³). Further person-related workplace measurement results (unknown number of measurements) in the tank wagon / dispatch area are below the detection limit of 27 mg/m³ (5 ml/m³).

The second company provided seven person-related measurement results of two different workplaces (see **Table 4.1**).

Table 4.1 Ethyl acetoacetate exposure at workplaces during production

Job category / activities	Year of measurement	Number of samples	Technical measures	Measurement data [mg/m³]
8h-TWA				
Production plant	2000	5 (p)	closed system	< 2.5
Short-term values				
Filling into barrels	2000	2 (p)	LEV	< 0.5 (90 min) < 0.6 (110 min)

p: personal sampling, LEV: local exhaust ventilation

Information on the collective of the exposed group is available for both companies. According to the first company 20 workers are exposed in total (10 continually, 10 intermittently). According to information provided by the second company one worker per shift (five shifts per day) is responsible for the production plant and six workers are employed in the area of filling and drumming operations.

The measurement results presented are assumed to be valid. The meaningfulness of the measurement results provided by the first company can only be assessed to a limited extent because workplaces and activities upon which the results are based are described only in general terms and because further detailed information on the duration and frequency of exposure is missing. A limited number of measurement results together with good descriptions of the workplaces are provided by the second company, which were taken for exposure assessment.

Based on the available measurement results 2.5 mg/m^3 (0.5 ml/m^3) is regarded to represent a reasonable worst-case situation for all activities during production and further processing in the chemical industry. In addition, the short-term value 0.6 mg/m^3 (0.1 ml/m^3, sampling time 110 min) obtained during filling of barrels is used for exposure assessment.

Manufacture of cosmetics which contain ethyl acetoacetate

Ethyl acetoacetate is used in the cosmetics industry, either directly, as an odorant (e.g. in after-shave lotion (Hoechst AG, 1993)) or in perfume oils (concentration < 5%), and as a solvent for nail varnish.

In these production sectors, closed systems can be assumed in most cases, where either continuous production or batch processing are employed. Since the produced quantities are unknown, it is unclear if production is continuous or batchwise. Workplace measurements and information on the duration and frequency of exposure as well as on the collective of exposed persons are missing. It is to be assumed that, in view of the very high sanitary requirements in these areas, the plants or workplaces (e.g. workplaces for filling operations) are equipped with suitable exhaust ventilation systems.

In general inhalative and dermal exposure in the chemical and in the cosmetic industry is to be assumed during sampling and analysis, weighing, transfer, filling and drumming, as well as during cleaning, maintenance and repair work. It is assumed, that the use of gloves is highly accepted within these industries. On account of the lack of information about the suitability of the materials, which are recommended by the producers, the estimation of dermal exposure levels according to the EASE model is used (see Section 4.1.1.2.4).

Manufacture of resins and paints

See Section 4.1.1.2.2.

4.1.1.2.2 Occupational exposure in the industrial further processing sector outside the large-scale chemical industry

Ethyl acetoacetate is used as a component in the manufacture of cleaners, washing detergents and air deodorants, of resins and paints, of colour films, as a synthetic natural flavouring substance in foodstuffs, for impregnating and coating of paper, and as a hardening accelerator in polyester paints.

Manufacture of cleaning products and air deodorants

Perfume oils (ethyl acetoacetate concentration < 5 %) may be used for purposes which include the manufacture of all-purpose cleaning products (12 % perfume oil, ethyl acetoacetate concentration < 0.5 %), washing detergents (20 % perfume oil, ethyl acetoacetate concentration < 1 %), and solid air deodorants (25 % perfume oil, ethyl acetoacetate concentration < 1.25 %, see Section 4.1.1.3).

There is only little information about the production of cleansers, washing detergents and air deodorants. Within the chemical industry, it is to be assumed that open systems are equipped with suitable local exhaust ventilation. In principle it cannot be excluded that open systems without suitable technical ventilation equipment are also employed and that no personal protective equipment is worn, e.g. in chemical small and medium sized enterprises (Voullaire, Kliemt, 1995). In a NIOSH walk-through survey (1980) through a plant which is engaged in the packaging of commercial aerosols and lotions, the compounding and packaging of a spot remover is described (Orris, Daniels, 1980). Some of the ingredients are hand charged into the mixer, which is closed afterwards.

During the production of cleansers, washing detergents and air deodorants inhalative (with and without LEV) and dermal exposure (via direct skin contact) of the workers is to be assumed during sampling and analysis, transfer, weighing, filling and drumming, as well as during cleaning, maintenance and repair work.

Manufacture of resins and paints

The production and distillative processing of resins take place in closed systems. Since it is not known whether the production methods are continuous or batchwise, batchwise is assumed. In the paint industry, ethyl acetoacetate is used as a hardening accelerator in unsaturated polyester paints. Paint dispersions are manufactured both in closed (e.g. stirrer mills) and open dispersers (e.g. three-roll mills), either continuously or in batch processes (Harnisch et al., 1982). Within the chemical industry, it is to be assumed that open systems are equipped with suitable local exhaust ventilation. In principle it cannot be excluded that open systems without suitable technical ventilation equipment are also employed and that no personal protective equipment is worn, e.g. in chemical small and medium sized enterprises (Voullaire, Kliemt, 1995). In the paint industry, full automatic production lines are seldomly used (e.g. for white dispersion paints); in view of the wide range of varieties, batch production may be assumed for most paint varieties (Goldschmidt et al., 1984). The ethyl acetoacetate content of the end-product is 1 - 5 %. Workplace measurements and information on the duration and frequency of exposure as well as on the collective of exposed persons are missing.

In 1986 a study was performed to determine exposure to organic solvents in 12 plants in the paint manufacturing industry in Germany (Auffarth, Häger, 1992). In more than 50 % the production systems were equipped with LEV and in app. 75 % with technical room ventilation.

The exposure data of 2-ethoxyethylacetate (p = 255 Pa), which is comparable to ethyl acetoacetate with regard to the vapour pressure and which is used in concentrations of approximately 2 – 10 % in paints and varnishes are used to estimate exposure to ethyl acetoacetate (comparison by analogy): the workplace measurement results (1986; n = 3) are < 5.5 mg/m³ (< 1 ml/m³). In the paint industry inhalative (with and without LEV) and dermal exposure (via direct skin contact) of the workers is to be assumed during sampling and analysis, filling and drumming, as well as during cleaning, maintenance and repair work.

Manufacture of foodstuffs and colour films

The scenarios are clustered because the activities which are relevant for exposure and the special quality requirements are comparable. Ethyl acetoacetate is used as a synthetic natural flavouring substance in foodstuffs (milk products, confectionary and bakery products). Milk products, confectionary and bakery products are produced industrially on the large scale in continuous, almost automatic production lines (Harnisch et al., 1986). The ethyl acetoacetate content of the end-product is < 150 ppm (Hoechst, 1996d).

Colour film manufacture comprises two basic process steps:

- The discontinuous production of photographic emulsions
- The continuous casting film process.

Because of the great sensitivity of photographic materials, individual process steps are performed within closed systems. On the contrary it is to be assumed that corresponding substances of content will be handled openly during preparing the reaction solutions needed to produce the emulsions. Workplace measurements and information on the duration and frequency of exposure as well as on the collective of exposed persons is missing.

Inhalative and dermal exposure of the workers is particularly possible during transfer, weighing, dosing work, filling procedures, and during cleaning, maintenance and repair activities. It is to be assumed that, in view of the particular quality requirements in these areas, the plant or workplaces (e.g. workplaces for filling operations) are equipped with suitable exhaust ventilation systems.

Use for impregnating and coating of paper

For the upgrading crude paper is coated and/or impregnated with different substances, after which it is dried. Open, partly housed continuous processes (impregnating machine, calender) are employed (Ahrens et al., 1996). In general for the preimpregnation and lamination of papers aqueous dispersions of plastics, solutions of synthetic resins, silicone or films are used (Baumann, Herberg-Liedtke, 1994). In these solutions and dispersions a content of ethyl acetoacetate of 5 % is assumed (comparable to that in resins and paints). Inhalative and dermal exposure of the workers is particularly possible during transfer, weighing and dosing work, during mixing procedures, as well as during cleaning, maintenance and repair activities.

For the risk assessment the inhalative exposure is also estimated through comparison by analogy. Therefore the following exposure data of 2-ethoxyethylacetate are used:

2-Ethoxyethylacetate is used for the upgrading of crude paper by impregnation and coating. Workplace measurements in this area of the paper industry are made by the Papiermacher-Berufsgenossenschaft and are stored in the system of documentation MEGA (measurement data about exposure to dangerous substances at the workplace). For 2-ethoxyethylacetate (p = 255 Pa) the workplace measurement results (1974 - 1993; n = 20) amount to a 90 % percentile of 17.5 mg/m³ (3.2 ml/m³). The measurement results are regarded as valid because of the sampling and analytical procedure and the measuring strategy used (TRGS 402, 1986) (Ahrens, Jöckel, 1996).

Use of polyester paints

Ready-to-use unsaturated polyester paints contain ethyl acetoacetate at concentrations of 1 - 5 % as a hardening accelerator. These paints are applied by roller, spraying and curtain coating processes, for furniture and automobile lacquering (including repair lacquering), and for corrosion prevention. The fields of application include the sectors of industrial fabrication and small and medium enterprises.

Inhalative and dermal exposure of workers against vapours and aerosols is possible during handling. Further dermal exposure is possible via direct skin contact during filling and cleaning work. Workplace measurements and information on the duration and frequency of exposure as well as on the collective of exposed persons are missing for the exposure scenarios described above.

In the context of a clinical multidisciplinary cross-sectional-study, 83 spray painters occupied in trade and industry have been examined to evaluate the exposure to paints, varnishes, dispersions, priming coats, thinners, etc. At selected and typical workplaces sampling was performed using an active and passive air sampling, lasting several hours. The volatile solvents were determined by gas chromatography. 2-ethoxyethylacetate (p = 255 Pa) is used in concentrations of app. 2 - 10 % in paints and varnishes for spray painting work. For the use of 2-ethoxyethylacetate during open spraying against water walls and in spray booths the workplace measurement results (n = 8) ranging from below the detection limit to 23.1 mg/m³ (4.3 ml/m³). The measurement results are regarded as valid because of the sampling and analytical procedure and the measuring strategy used (TRGS 402, 1986; Triebig, Schaller, 1991).

4.1.1.2.3 Occupational exposure in the skilled trade sector

Use of polyester paints and cosmetics

Polyester paints can be employed in the skilled trade sector to coat mineral grounds, for corrosion prevention and for automobile and furniture lacquering. Automobile repair lacquering in car repair shops without a spray booth is limited. In general the lacquering is carried out in a more separate area. The process itself is mainly limited to a few minutes. In this short duration significant exposure to solvents were not determined (Auffarth, Hebisch, Rentel, 1997).

The inhalative and dermal exposure of workers is to be expected during handling of the coating materials and during spray painting. Workplace measurements and information on the duration and frequency of exposure as well as on the collective of exposed persons are missing.

Use of cosmetics

Ethyl acetoacetate is used as an odorant (e.g. in after-shave lotion (Hoechst AG, 1993)) or in perfume oils (concentration < 5 %), and as a solvent for nail varnish in unknown concentrations. Inhalative and dermal exposure of workers is to be expected in the hairdressing and cosmetic trade during manual application of the end products.

Use of cleaning agents

Perfume oils (ethyl acetoacetate concentration < 5 %) may be used for all-purpose cleaning products (12 % perfume oil, ethyl acetoacetate concentration < 0.5 %) or washing detergents (20 % perfume oil, ethyl acetoacetate concentration < 1 %). All-purpose cleansers are commercially applied to clean surfaces, e.g. floors and windows within buildings (business and administration). In general aqueous solutions of 1:10 (0.05 % ethyl acetoacetate) or 1:100 (0.005 %) are used; in particular cases for very dirty layers the cleansers are used undiluted. On account of the low concentrations of ethyl acetoacetate in aqueous solutions the partial vapour pressure is calculated in a first assumption (Raoult`s law) to be < 1 Pa. The inhalative exposure is calculated by EASE. Immediate skin contact with the diluted solution will occur often, if no PPE is used. Contamination with concentrated solutions will happen more seldom, when concentrated cleanser are manually applied during transfer for dilution or cleaning of very dirty objects.

4.1.1.2.4 Estimation of the exposure according to the EASE model

The estimation of the level of inhalative exposure performed in accordance with the EASE model produces the following results:

The version EASE for Windows 1995 was used.

Inhalative exposure

Inhalative exposure during manufacture and use in the chemical industry and the production of formulations with local exhaust ventilation (LEV)

(e.g. as cosmetics, resins and paints, cleaners, washing detergents, air deodorants, foodstuffs and colour films)

Input parameters: T = 20°C;
closed system
significant breaching
LEV present

Estimated exposure level: **3 - 16 mg/ m^3 (0.5 - 3 ml/m^3).**

Considering the frequency and duration for the production of formulations (e.g. as resins and paints, cleaners, washing detergents and air deodorants) of app. 2 hours daily, the exposure level is estimated to:

0.75 - 4 mg/m^3 (0.13 - 0.75 ml/m^3).

Inhalative exposure during manufacturing of formulations without LEV

(e.g. additive for paper laminating and impregnating, resins and paints, cleansers, washing detergents, air deodorants)

Input parameters: T = 20 °C;
non dispersive use
direct handling
dilution ventilation present

Estimated exposure level: **54 - 270 mg/m^3 (10 - 50 ml/m^3).**

Considering the frequency and duration for the production of formulations (e.g. as resins and paints, cleansers, washing detergents and air deodorants) of app. 2 hours daily, the exposure level is estimated to: **14 - 68 mg/m^3 (2.5 - 12.5 ml/m^3).**

Inhalative exposure during use of cleansers without LEV

(e.g. all-purpose cleaners) considering the content of ethyl acetoacetate in aqueous cleaning solutions, which are normally used, of app. 0.1%, the partial vapour pressure decreases to < 1 Pa.

Input parameters: T = 20 °C;
p < 1 Pa
wide dispersive use
direct handling
dilution ventilation present

Estimated exposure level: **0 - 0.6 mg/m^3 (0 - 0.1 ml/m^3).**

Inhalative exposure during spray painting (with LEV)

Input parameters: T = 20 °C;
aerosol-formed
non dispersive use
LEV present

Estimated exposure level: **540 – 1,080 mg/m^3 (100 - 200 ml/m^3).**

Considering the content of ethyl acetoacetate in polyester sprays of max. 5 %, the exposure level is estimated to: 27 - 54 mg/m^3 (5 - 10 ml/m^3).

Inhalative exposure during spray painting (without LEV)

Input parameters: T = 20 °C;
aerosol-formed
wide dispersive use
LEV absent

Estimated exposure level: **2,697 – 5,394 mg/m^3 (500 - 1000 ml/m^3).**

Considering the frequency and duration of handling of app. 2 hours daily and the content of ethyl acetoacetate in polyester sprays of max. 5 %, the exposure level is estimated to:

34 - 67 mg/m^3 (6.25 - 12.5 ml/m^3).

Dermal exposure

Dermal exposure during manufacture and use in the chemical industry and the production of formulations

(e.g. as cosmetics, resins and paints, cleaners, washing detergents, air deodorants, foodstuffs and colour films):

Input parameters: T = 20°C;
closed system
significant breaching (or non-dispersive use)
direct handling
intermittent

Estimated exposure level: **0.1 - 1 mg/cm^2/day**.

For the estimation of the dermal exposure during use of formulations like resins and paints, or solutions and dispersions for the impregnating and coating of paper in the industrial area the same input parameters as above are used. Considering the content of 5 % ethyl acetoacetate (for paper laminating and pre-preg assumed) the estimated exposure level is reduced to:

0.005 - 0.05 mg/cm^2/day.

Dermal exposure during use of cosmetics (e.g. after-shave lotion) and during spray painting

Input parameters: T = 20°C;
wide dispersive use
direct handling
intermittent

Estimated exposure level: **1 - 5 mg/cm^2/day**.

Considering the content of ethyl acetoacetate in after-shave lotion of app. 1.25 %, the exposure level is estimated to: **0.0125 - 0.0625 mg/cm^2/day**.

Considering the content of ethyl acetoacetate in paints of max 5 %, the exposure level for spray painting of polyester paints is estimated to:

0.05 - 0.25 mg/cm^2/day.

Dermal exposure during use of cleansers (e.g. all-purpose cleaners)

Input parameters: T = 20°C;
wide dispersive use
direct handling
extensive

Estimated exposure level: **5 - 15 mg/cm^2/day.**

Considering the content of ethyl acetoacetate in cleaning solutions of app. 0.05 %, the exposure level is estimated to: **0.0025 - 0.0075 mg/cm^2/day**.

4.1.1.2.5 Other exposure data

No exposure data of ethyl acetoacetate from other sources are known.

Analogous data were provided by The Netherlands (TNO, 1998). Dermal exposure during spray painting of polyester paints was investigated by adding a non-volatile fluorescent whitening agent and detection using UV-light.

The airless spray painting technique was used. A total of 12 painters (3 companies, 4 painters each) was asked to paint the outside of a container twice (two separate sampling periods). Five of the painters also painted the inside of the container once (a third sampling period). Only the actual spray painting was sampled. Mixing of paint and filling of the spraying equipment was not part of the sampling period, so only exposure due to actual painting was assessed.

Extrapolating the results to a component being at 10 % in paints, dermal exposure amounts to ca. 500 mg on a surface area of approx. 600 cm² (hands and part of the head). With regard to 5 % ethyl acetoacetate, the dermal exposure level would reduce to 300 mg/cm².

4.1.1.2.6 Integrated Assessment

General

Information on the duration and frequency of exposure is generally missing. Information on the collective of exposed persons has been provided by two producers for the production and filling area. Comparisons by analogy and the EASE model have been used to estimate exposure levels of ethyl acetoacetate for the different exposure scenarios.

Manufacture and further processing in the chemical industry and cosmetic industry

The scenarios are clustered in view of the very high sanitary requirements for the production of cosmetics. The submitted measurement results (< 2.5 mg/m^3, < 0.5 ml/m^3) for manufacture are assumed to be valid. The estimate of inhalation exposure based on the EASE model ranges at 3 - 16 mg/m³ (0.5 - 3 ml/m³). This exposure range is valid for substances with vapour pressures between 1 – 1,500 Pa. Taking into account that ethyl acetoacetate has a vapour pressure of 100 Pa which is located at the lower end of the range of vapour pressures, it is concluded that the model estimate confirms the measurement results. The information on the collective of exposed persons implies that a small number of workers is continually exposed. At present, for the

assessment of risks in the chemical industry during inhalative continuous exposure an 8h-TWA of < 2.5 mg/m^3 (< 0.5 ml/m^3) based on measurement results of one company is to be used.

On account of the lack of information about the suitability of the materials of the gloves which are recommended by the producers, the estimation of dermal exposure levels according to the EASE model of 0.1 - 1 mg/cm^2/day is used (see Section 4.1.1.2.4), regardless that the materials used could provide a limited protection. For the assessment of risks in the chemical industry during dermal repeated exposure with regard to an exposed area of 420 cm^2 (palms of two hands) an exposure level of 42 - 420 mg/person/day is used.

Use of perfume oils in the manufacture of cleaning agents, resins and paints

There is only little information about the production of cleansers, washing detergents and air deodorants. For the manufacturing of cleaning products two scenarios are assumed with and without LEV. As it is shown in a NIOSH walk-through survey (1980) during compounding and packaging of a spot remover (Orris, Daniels, 1980) some of the ingredients are hand charged into the mixer, which is closed afterwards. Additionally it cannot be excluded that no personal protective equipment is worn, e.g. in chemical small and medium sized enterprises (Voullaire, Kliemt, 1995).

Perfume oils (ethyl acetoacetate concentration < 5 %) may be used for purposes which include the manufacture of all-purpose cleaning products (ethyl acetoacetate concentration < 0.5 %), washing detergents (ethyl acetoacetate concentration < 1 %), and as solid air deodorants (ethyl acetoacetate concentration < 1.25 %, see Section 4.1.1.3).

The production and processing of resins take place in closed systems of paints - ethyl acetoacetate is used as a hardening accelerator in unsaturated polyester (UP) paints - both open and closed systems are employed (Harnisch et al., 1982). It is not known if the production methods for UP are continuous or batchwise.

Within the chemical industry, it is to be assumed that open systems are equipped with suitable local exhaust ventilation. In principle it cannot be excluded that open systems without suitable technical ventilation equipment are also employed and that personal protective equipment is not worn, e.g. in chemical small and medium sized enterprises (Voullaire, Kliemt, 1995). In 1986 a study was performed to determine exposure to organic solvents in 12 plants in the paint manufacturing industry in Germany (Auffarth, Häger, 1992). In more than 50 % the production systems were equipped with LEV and in app. 75 % with technical room ventilation.

The ethyl acetoacetate content of the end product is 1 - 5 %. For the both industries workplace measurements and information on the duration and frequency of exposure as well as on the collective of exposed persons are missing.

Exposure data of 2-ethoxyethylacetate (p = 255 Pa), which is comparable to ethyl acetoacetate with regard to the vapour pressure and which is used in concentrations of app. 2 - 10 % in paints and varnishes is used to estimate exposure to ethyl acetoacetate (comparison by analogy): based on workplace measurement results (1986; n = 3) being < 5.5 mg/m³ (< 1 ml/m³) 6 mg/m³ is assumed to be an appropriate exposure level for the scenario of paint production.

Exposure is also estimated in application of the EASE model. For workplaces with LEV a potential exposure (8 h-TWA) of 3 - 16 mg/m³ (0.5 - 3 ml/m³) results and for workplaces without LEV of 54 - 270 mg/m^3 (10 - 50 ml/m^3). Because batch production may be assumed for most paint varieties (Goldschmidt et al., 1984) and cleansing agents exposure levels are expected to be lower, since the duration per working day of activities (e.g. filling work) associated with

exposure is shorter than the shift length. For e.g. filling activities a duration of two hours/day is reasonable, the exposure level is reduced to 14 - 68 mg/m^3 (2.5 - 12.5 ml/m^3; without LEV).

For the assessment of risks during dermal exposure the estimation according to the EASE model (0.1 - 1 mg/cm^2/day) with regard to an exposed area of 420 cm^2 (palms of two hands) an exposure level of 42 - 420 mg/person/day is used. For the manufacturing of cleaning agents and air deodorants the exposure level is reduced to 2 - 21 mg/person/day considering a concentration of ethyl acetoacetate of 5 % in the perfume oil used as educt.

Manufacture of foodstuffs and colour films

The scenarios are clustered because the activities which are relevant for exposure and the special quality requirements are comparable. In these sectors, it is to be assumed that the substance is handled openly during certain work activities such as dosing and filling, the preparation of solutions, and during cleaning, maintenance and repair activities. It is also to be assumed that, in view of the special quality requirements, the plant or workplaces (e.g. workplaces for filling operations) are equipped with suitable exhaust ventilation systems, and that personal protective equipment is worn.

The risks of inhalative exposure are to be assessed on the basis of an 8h-TWA of 3 - 16 mg/m³ (< 0.5 - 3 ml/m³) which is estimated in application of EASE model. Taking into account that the duration per working day of activities (e.g. filling) associated with exposure is shorter than the shift length, inhalative exposure is assumed to be lower.

On account of the lack of information about the suitability of the materials of the gloves which are recommended by the producers, the estimation of dermal exposure levels according to the EASE model of 0.1 - 1 mg/cm^2/day is used (see Section 4.1.1.2.4). For the assessment of risks in the foodstuffs and colour film industry during dermal repeated exposure with regard to an exposed area of 420 cm^2 (palms of two hands) an exposure level of 42 - 420 mg/person/day is used.

Use as an additive in formulations for impregnating and coating of paper

In general for the preimpregnation and lamination of papers aqueous dispersions of plastics, solutions of synthetic resins, silicone or films are used (Baumann, Herberg-Liedtke, 1994). In these solutions and dispersions a content of ethyl acetoacetate of 5 % is assumed (comparable to that in resins and paints). In this sector it may be assumed that the solutions are handled openly during certain work activities such as dosing and filling. During the drying process the substance can also partially evaporate. It cannot be excluded that PPE is not worn.

The inhalative exposure is estimated through comparison by analogy. Data is taken from the application of 2-ethoxyethylacetate (p = 255 Pa) for impregnating and coating of paper. Workplace measurement results amount to a 90 % percentile of 17.5 mg/m³ (3.2 ml/m³) (Ahrens et al., 1996), which is to be assumed as the 8h-TWA for assessing the risks of inhalative exposure. For the assessment of risks during dermal exposure the estimation according to the EASE model (0.1 - 1 mg/cm^2/day) with regard to an assumed concentration of ethyl acetoacetate of 5 % in the solutions (0.005 - 0.05 mg/cm^2/day) and an exposed area of 420 cm^2 (palms of two hands) an exposure level of 2 - 21 mg/person/day is used.

Use as a hardening accelerator in polyester paints

In view of the diverse uses of polyester paints (industrial production, small and medium enterprises), when estimating inhalative exposure to vapours and aerosols workplaces without exhaust ventilation systems must be taken into account. In the industrial area in general paint booths are employed. Automobile repair lacquering in car repair shops in the skilled trades is limited to cases for which only a few minutes are needed. In this short duration singnificant exposure to solvents were not determined (Auffarth, Hebisch, Rentel, 1997). For the estimation of the dermal exposure, more or less frequent direct skin contact with the preparations must be assumed. It cannot be excluded, that PPE is not worn.

Inhalative and dermal exposure to vapours and aerosols must be assumed during use, dermal exposure during filling and cleaning of the used equipment (no measured values are available).

The inhalative exposure is estimated through comparison by analogy. Using 2-ethoxyethyl acetate (p = 255 Pa) in paints and varnishes at concentrations of approx. 2 - 10 %, workplace measurements during spray painting work in spray booths reveal 8h-TWA-values in the range of below the detection limit up to 23.1 mg/m³ (n = 8, Triebig et al., 1991). In order to assess the risks of inhalative exposure to aerosols during spray painting work, an 8h-TWA of 20 mg/m³ (3.7 ml/m³) should be used. The estimation for use of LEV according to the EASE model (540 - 1080 mg/m³) with regard to a concentration of max. 5 % is with 27 - 54 mg/m³ (5 - 10 ml/m³) in the same order of magnitude.

For the scenario of spray painting without LEV, outside of spray booth, which may occur more often in the skilled trade area, measurement results are not known. For the assessment of the risks the estimation for non-use of LEV according to the EASE model (2,697 – 5,394 mg/m³) with regard to a concentration of max. 5 % (135 - 270 mg/m³) and a duration of exposure of app. 2 hours of 33.5 - 67 mg/m³ (6.25 - 12.5 ml/m³) is used.

For the assessment of risks during dermal repeated exposure the estimation according to the EASE model (0.1 - 1 mg/cm^2/day) with regard to a concentration of max. 5 % (0.005 - 0.05 mg/cm^2/day) and an exposed area of 1,300 cm^2 (hands and forearms) an exposure level of 6- 65 mg/p/day is used. This level relates to dermal exposure for spraying in spray booths with high levels of protection. If the pattern of control is lower the estimation increases to 1 – 5 mg/cm^2/day, resulting in an exposure level of 65 - 325 mg/person/day. This value is in the same order of magnitude as the result obtained in a study on dermal exposure performed by Nl (for 5 % ethyl acetoacetate: 300 mg on a surface area of 600 cm²). This comparison is limited because, beside other parameters, the study considers dermal exposure to the head and hands, whereas the EASE estimate relate to exposure to hands and forearms and do not consider additional exposure to other parts of the body.

Use of cleaning agents

Perfume oils (ethyl acetoacetate concentration < 5 %) may be used for all-purpose cleaning products (12 % perfume oil, ethyl acetoacetate concentration < 0.5 %) or washing detergents (20 % perfume oil, ethyl acetoacetate concentration < 1 %). All-purpose cleaners are commercially applied to clean surfaces, e.g. floors and windows within buildings (business and administration). In general aqueous solutions of 1:10 (0.05 % ethyl acetoacetate) or 1:100 (0.005 %) are used; in particular cases for very dirty layers the cleaners are used undiluted. On account of the low concentrations of ethyl acetoacetate in the aqueous solutions the partial vapour pressure is calculated in a first assumption (Raoult`s law) to be < 1 Pa. For the assessment of risks during inhalative repeated exposure the estimation according to the EASE

model (0 - 0.6 mg/m^3) is used. During dermal repeated exposure the estimation according to the EASE model yields 5 - 15 mg/cm^2/day. With regard to the concentration of 0.05 % (0.0025 - 0.0075 mg/cm^2/day) and an exposed area of 1,300 cm^2 (hands and parts of the forearms) an exposure level of 3 - 10 mg/person/day is used.

No other information is available on the use of ethyl acetoacetate.

Use of cosmetic products

Ethyl acetoacetate is used as a perfume oil or as a solvent in cosmetics such as after-shave lotion or nail varnish. The inhalative exposure of workers in the cosmetic trade (e.g. professional beauty specialist, hairdresser) is expected to be low because of the relative low vapour pressure of the pure substance, the small amounts used and the short duration of use.

The dermal exposure for the handling of nail lacquers is also assumed to be low. With regard of the properties of the lacquers, the workers, in general, will try to avoid skin contact. Beside of that, the area of contact will be very small and the duration and frequency is assumed to be short-term and occasional. The handling of after-shave lotions may be more often. During dermal repeated exposure the estimation according to the EASE model yields 1 - 5 mg/cm^2/day. With regard to the concentration of 1.25 % (0.0125 - 0.0625 mg/cm^2/day) and an exposed area of 420 cm^2 (palms of two hands) an exposure level of 5 - 26 mg/person/day is used.

Summary of exposure data relevant for workplace risk assessment

The following table shows the exposure data of ethyl acetoacetate which are relevant for occupational risk assessment:

Table 4.2 Exposure data relevant for occupational risk assessment

Exposure scenario	Form of exposure	Activity	Inhalative exposure			Dermal exposure			
			Duration and frequency	Shift average [mg/m³]	Method	Level of exposure [mg/cm²/day]	Exposed area [cm²]	Shift average [mg/p/day]	Method
Chemical industry									
Manufacturing (liquid) and further processing as a chemical intermediate (pharmaceuticals, pesticides, dyes and pigments)	vapour (100 Pa) (solution) (> 99 %)	drumming transfer cleaning maintenance	shift length, daily	< 2.5 (with LEV)	workplace measurements (n = 5)	0.1 - 1	420 (palms of two hands)	42 - 420	EASE
Manufacture of cosmetics (especially nail varnish, after-shave lotion)	vapour (100 Pa) (solution)	transfer weighing filling drumming	shift length, daily	see above	expert judgement	0.1 - 1	420 (palms of two hands)	42 - 420	EASE
Industrial area									
Use of perfume oils (content < 5 %) in the manufacture of cleaning products (content < 1. %) and air deodorants (< 1.25 %)	vapour (solution)	transfer weighing filling drumming	batch processing 2 hours/daily	0.75 - 4 (with LEV) 14 - 68 (without LEV) [2)]	EASE exposure shorter than shift length	0.005 - 0.05	420 (palms of two hands)	2 - 21	EASE
Manufacture of polyester paints, use as an additive in resins and as hardening accelerator (formulation companies)	vapour (solution)	transfer weighing filling drumming	batch processing 2 hours/daily	< 6 0.75 - 4 (with LEV) 14 - 68 (without LEV) [2)]	comparison by analogy[1)] EASE, exposure shorter than shift length	0.1 - 1	420 (palms of two hands)	42 - 420	EASE

Table 4.2 continued overleaf

Table 4.2 continued

Exposure scenario	Form of exposure	Activity	Inhalative exposure			Dermal exposure			
			Duration and frequency	Shift average [mg/m^3]	Method	Level of exposure [mg/cm^2/day]	Exposed area [cm^2]	Shift average [mg/p/day]	Method
Manufacturing of foodstuffs and colour films together because of comparable standards of cleanliness	vapour (solution)	transfer weighing filling drumming	shift length, daily	3 -16 (with LEV)	EASE	0.1 - 1	420 (palms of two hands)	42 - 420	EASE
Use as an additive in formulations, for impregnating and coating of paper assumption: 5 %	vapour (solution)	transfer weighing filling mixing	shift length, daily	17.5 (90th-%)	comparison by analogy[1)]	0.005 - 0.05	420 (palms of two hands)	2 - 21	EASE
Use as a hardening accelerator in polyester paints during spray painting (content 1 - 5 %)	vapour (solution)	spray painting	shift length, daily	app. 20 27 - 54	comparison by analogy[1)] EASE	0.005 - 0.05	1 300 (hands and part of the forearms)	6 - 65	EASE

Table 4.2 continued overleaf

Table 4.2 continued

Exposure scenario	Form of exposure	Activity	Inhalative exposure			Dermal exposure			
			Duration and frequency	Shift average [mg/m³]	Method	Level of exposure [mg/cm²/day]	Exposed area [cm²]	Shift average [mg/p/day]	Method
Skilled trade									
Use as hardening accelerator in polyester paints for repair lacquering during spray painting (content 1 - 5 %)	vapour (solution)	spray painting	a few minutes, frequency unknown; assumed: several times per day: 2 hours/daily	33.5 - 67	EASE	0.05 - 0.25	1,300 (hands and part of the forearms)	65 - 325	EASE
Use of cleansers (all-purpose cleanser, washing detergents) content: 0.05 %	vapour (solution)		shorter than shift length, daily	0 - 0.6	EASE	0.0025 - 0.0075	1,300 (hands and part of the forearms)	3 - 10	EASE
Use of cosmetics (nail -lacquers, after-shave lotion) content: assumed 1 %	vapour (solution)		short-term, occasionally (nail-lacquers)	low	expert judgement	low		low	expert judgement
			short-term, daily (after-shave lotion)	low	-	0.0125 - 0.0625	420 (palms of two hands)	5 - 26	EASE

[1] Analogous data form 2-ethoxyethylacetate, p = 255 Pa, content 2 – 10 %

[2] All values are taken forward for risk assessment

4.1.1.3 Consumer exposure

In the main fields of use, ethyl acetoacetate is almost exclusively used as an intermediate and is therefore no longer present in the final products. In some products, it may be used as a flavouring substance (in concentrations of <10 ppm in milk products, confectionery and bakery products) and as an odorant in perfume oils in concentrations of up to 5 %. Perfume oils are used in various products (e.g. body care products, detergents and sanitary cleaning products, room deodorants).

Remark

For estimation of consumer exposure, standard assumptions of typical uses have priority; where this is not practicable, more arbitrary assumptions are used.

Under these variable circumstances, it is not possible to estimate an exact individual exposure. Thus, it seems to be more useful to declare exposure limits within the possible nanogram, microgram or milligram ranges (lower range = 1-10, middle range = 10-100, upper range = 100-1,000).

Under conditions of proper use of the preparations, the following exposure will result for the consumer:

Dermal exposure

Cosmetics

Eau de Cologne contains 5 % perfume oil consisting of 5 % odorant. When 0.75 g of eau de Cologne is used 5 times a day, an exposure of the consumer to approx. 9 mg odorant per day will result; exposure of the consumer is in the upper µg range/kg body weight and day.

Eau de perfume contains 15 % perfume oil consisting of 5 % odorant. When 5 drops of eau de perfume per day are applied, a dermal exposure of the consumer to the odorant in the medium µg range/kg body weight and day will result.

Creams and ointments contain less than 1 % perfume oil consisting of 5 % odorant. Body lotion applied in a quantity of 16 g lotion/day will result in an exposure of the consumer to the odorant in the upper µg range/kg body weight and day. When 0.8 g face cream is used per day, dermal exposure of the consumer to the odorant will be in the lower µg range/kg body weight and day (Colipa, 1989; Wissenschaftlicher Ausschuß, 1994; Umbach, 1995; BgVV, 1996).

Detergents and other household products

Odorants are also added to detergents and other household products. Dermal exposure of the consumer may result from these products (Velvart, 1993; BgVV, 1996).

Inhalatory exposure

The EPA model SCIES is used for assessing the inhalatory exposure of the consumer.

All purpose cleaners:

Inhalatory exposure of the consumer to the odorant is in the medium µg range/kg body weight and day when a fluid all-purpose cleaner is used whose content of perfume oil is 12 % (of which 5 % accounts for odorant) and is applied under standard conditions.

Detergents

When using a detergent under standard conditions in the washing machine (20 % perfume oil containing 5 % odorant), an inhalatory exposure of the consumer to the odorant in the upper µg range/kg body weight and day will result.

Room deodorant

When using a solid room deodorant (25 % perfume oil containing 5 % odorant) under standard conditions, consumer exposure to the odorant will be in the lower µg range/kg body weight and day.

Cosmetics and household products

An inhalatory exposure of the consumer to the odorant (e.g. by the use of sprays) is also possible.

Conclusion

Taking into account that ethyl acetoacetate is no longer present in most consumer products, a residual exposure cannot be excluded by use of these consumer products. This exposure may be in the upper range µg/kg bw and day. Although the sum of all estimated possible exposures is higher by way of calculation it seems unlikely that exposure in reality will exceed this range.

4.1.1.4 Humans exposed via the environment

In accordance with the TGD, the indirect exposure of man to ethyl acetoacetate via the environment, e.g. via food, drinking water and air, must be determined. In the form of a worst-case scenario, the most significant point source (in this case the company involved in the formulation of paints and lacquers) is considered for calculation purposes. This result is then compared with a second calculation which is based on the regional background concentrations (see Section 3.1.7).

The results of these calculations with the corresponding input values are summarized in Appendix 3. It is necessary to note, however, that the utilized calculation model is as yet only provisional. It requires revision as soon as further information is available.

The following input parameters were selected:

Table 4.3 Input parameters

	PEClocal scenario (greatest point source)	regional background concentrations
Concentration in soil	$3.9 \cdot 10^{-5}$ mg/kg	$1.8 \cdot 10^{-6}$ mg/kg
Concentration in the surface water	0.022 mg/l	$4.0 \cdot 10^{-5}$ mg/l
Concentration in the atmosphere	$2.4 \cdot 10^{-4}$ mg/m3	$3.7 \cdot 10^{-7}$ mg/m3
Concentration in the ground water	$1.1 \cdot 10^{-5}$ mg/l	$5.0 \cdot 10^{-6}$ mg/l

The resultant daily doses for the substance are as follows:

- DOSEtot = 0.787 µg/kg body weight day (local scenario)
- DOSEtot = 0.00141 µg/kg body weight day (regional background concentrations)

The calculated uptake quantities result via the following routes:

Table 4.4 Uptake quantities

Uptake route	% of total uptake	
	local	regional
drinking water	79.9	80.9
fish	1.5	1.5
plant shoot	11.9	10.1
root	0.07	1.9
meat	$7.0 \cdot 10^{-4}$	$6.8 \cdot 10^{-4}$
milk	0.01	0.01
air	6.7	5.6

Drinking water is the most significant route of uptake, when taking both a local and regional approach to the calculation of the indirect exposure.

4.1.2 Effects assessment: Hazard identification and Dose (concentration) - response (effect) assessment

4.1.2.1 Toxico-kinetics, metabolism and distribution

Available data with respect to toxicokinetics are very limited.

Relevant inhalatory exposure is generally possible due to the vapour pressure of ethyl acetoacetate (approximately 1 hPa at 20°C) being considered of toxicological relevance. Water solubility (about 125 g/l at 16°C) and partition coefficient (log Pow = 0.25) indicate good bioavailability of the substance.

It may be anticipated that ethyl acetoacetate is partially cleaved already in the gastrointestinal tract due to acidic pH values or by bacterial activity. In a first metabolic step the absorbed ethyl acetoacetate will be hydrolysed into 3-oxobutanoic acid and ethanol by unspecific esterases of blood. The acid moiety is an endogenous product within the lipid metabolism and is further metabolized predominantly to carbon dioxide and water. As well ethanol will be metabolized on known pathways.

After administration of radioactive labelled C^{14}-ethyl acetoacetate into the duodenum of male rabbits 1.5% of the applied radioactivity were found in bile as keto bodies within 24 hours (Asagoe et al., 1968).

In a further study male rats were exposed by gavage to calculated doses of 4.2, 8.4 and 33.7 g/m^2 body surface/day over 4 to 6 days (corresponding to 0.66, 1.31 and 5.26 g/kg bw). Independent

of dosage within 24 hours post dosing 1.5 to 15.1% of the applied dose was excreted as acetone in the urine. The excreted amount of acetone increased fourfold from first to last application in low and medium dose groups. In the high dose group acetone excretion remained at 6% of the applied dose over the whole period (Deuel et al., 1936).

For predicting in humans rates of ester hydrolysis using data derived from animal studies one has to consider that esterase activities in human plasma are generally lower than those p.e. in the rat. This conclusion is bases on species differences in hydrolysis of different substances such as ester-type drugs and prodrugs. E.g., the esterase activities in rat plasma for phenylacetate, paraoxon, and fluazifop-butyl were generally greater than those found in humans (McCracken et al., 1993). Furthermore, the esterase activity in rat whole blood for TEI-9090 (isocarbacyclin methyl ester) was approximately 400 times higher than in human whole blood (Minagawa et al., 1995). Moreover, the hydrolysis rate of the prodrug glycovir in whole blood of rats was 15-fold higher compared to that in man (Cook et al., 1995). Therefore it has to be assumed, that the stability (half-life) of systemically available ethyl acetoacetate is clearly higher in humans than in rats.

4.1.2.2 Acute toxicity

Animal data

Oral

In rats, oral LD50 values of 3,980 mg/kg bw (Smyth et al., 1949) and higher (12,300 mg/kg bw for males and 10,800 mg/kg bw for females) are reported. In a test with 5 male and 5 female rats per dose, rats dosed 2-4 g/kg bw exhibited moderate diarrhea, rats dosed 8 g/kg bw showed moderate to severe diarrhea. Doses of 10 g/kg bw killed 1/5 male and 2/5 female rats (clinical signs: rapid erratic respiration, lethargy, severe diarrhea, ruffled and unkempt coats). After forced feeding of 16 g/kg bw all rats died within 30 min (Bio-Toxicology Laboratories, 1975).

Inhalation

Only an abstract of a test is available (Smyth et al., 1949). Following 8 hours of exposure to saturated substance vapours, no deaths in rats were reported.

Dermal

The dermal LD50 is reported to exceed 10 ml/kg bw (10.3 g/kg bw) (Smyth et al., 1949); no further data are available.

Human data

Human data are not available.

Conclusion

Data on human experience with the substance are not available.

Ethyl acetoacetate has demonstrated low toxicity after oral application, with oral LD50s for rats in the range of 3,980-12,300 mg/kg bw. There are no valid data on toxicity by inhalation. However, the inhalation toxicity seems to be low as judged on the basis of a poorly reported test with rats surviving an 8-hour exposure to saturated substance vapours. Acute dermal toxicity in the rabbit is low, the dermal LD50 value was detected to exceed 10 ml/kg (10.3 g/kg) bw.

4.1.2.3 Irritation

Animal data

Ethyl acetoacetate has demonstrated no or only mild irritating properties to the skin of rabbits (Smyth et al., 1949), depending on the duration of exposure and the dose: three albino rabbits were exposed semi-occlusively to 0.5 ml of the substance for 4 hours. None of the animals exhibited any sign of irritation (Hoechst AG, 1983a).

The substance is reported to cause mild irritation in the eyes of rabbits (Smyth et al., 1949). In a Draize test according to OECD guidelines, three albino rabbits were tested with 0.1 ml of the substance each. None of the animals exhibited effects on the cornea, but moderate conjunctival irritation was detected (reversible within 2 days). 1/3 animals showed slight irridial redness, reversible within 3 days (Hoechst AG, 1983b).

Human data

Human data are not available.

Conclusion

Human data on local irritant substance properties are not available.

Ethyl acetoacetate exhibits mild irritating properties to the skin and eyes of rabbits, depending on the duration of exposure and the dose.

4.1.2.4 Corrosivity

Animal data

Ethyl acetoacetate exhibits only mild irritating properties to the skin and eyes of rabbits, depending on the duration of exposure and the dose (cf. Section 4.1.2.3).

Human data

Human data are not available.

Conclusion

Human data on local irritant substance properties are not available.

Ethyl acetoacetate exhibits only mild irritating properties to the skin and eyes of rabbits. It is concluded that ethyl acetoacetate is not a local corrosive substance.

4.1.2.5 Sensitisation

Animal data

No valid data available.

Human data

Valid human data are not available.

In a human maximization test 26 volunteers did not show any positive skin reactions after topical challenge treatment with 8 % ethyl acetoacetate in petrolatum (Opdyke, 1974; only abstract available).

Conclusion

Valid human or animal data are not available.

Taking into account the long experience with human exposure to the substance (especially as an ingredient in cosmetic nail lacquers) and the absence of any reports on contact allergy in exposed persons, ethyl acetoacetate is not supposed to exhibit skin sensitizing properties.

4.1.2.6 Repeated dose toxicity

Animal data:

Oral administration

In a valid repeated dose toxicity study (OECD 407, Hazleton, 1991), Sprague-Dawley rats (5 animals/sex/group) were administered by gavage with doses of 50, 225, and 1,000 mg/kg bw/d of ethyl acetoacetate (purity 99.6%) for 4 consecutive weeks. After the end of treatment, additional groups of control animals and of high dose animals were observed for a 2-week treatment-free period. There were no deaths. In week 2, approximately half the high dose animals were salivating immediately after dosing. In weeks 3 and 4, salivation was present in all high dose animals. Body weight gain and food consumption were comparable in treated animals and in controls. Ophthalmology revealed no eye lesions. No treatment-related difference in hematology and clinical chemistry parameters were found. Organ weights did not differ in dosed animals from that of the controls. No treatment-related macroscopic and microscopic findings were observed. The dose level of 1,000 mg/kg bw/d was identified as the NOAEL in this study.

A 28-day oral toxicity study in rats (Olac: Sprague-Dawley strain) was conducted by BIBRA (1988, Cook et al., 1992). Groups of 16 male and 16 female rats were fed diet containing ethyl acetoacetate at a concentration equivalent to 0, 100, 300, and 1,000 mg/kg bw/d of ethyl acetoacetate (encapsulated by spray drying with gum arabic). Control animals received diet with spray-dried gum arabic. Because there were no data on the test substance purity and study report did not include appendices on individual animal data, this study was evaluated as not valid but as additional information. No changes in body weight gain or diet consumption were related to treatment. A small increase in the hematological parameter: mean cell volume (MCV) was recorded in treated male and female rats. No other red cell parameters showed differences in treated males from that of control males. Females of the mid and high dose groups showed higher values for hematocrit and reduced MCHC (Mean Corpuscular Hemoglobin Concentration) values than control females. Red cell counts were increased in high dose females compared to controls. However, all changes were within the normal range and were not considered to be toxicologically significant. All serum chemistry parameters were within normal limits and isolated differences found were not considered to be treatment related. The relative weights of full and empty caecum were increased in high dose males but histopathology was normal. In high dose females there was a tendency to minimal lower caecum weights without gaining significance. BIBRA discussed caecum weights effects in males to be due to a functional hypertrophy. In view of the absence of any histopathological change in the caecum, it was considered of no toxicological significance. Histopathological examination revealed an increased incidence of nephrocalcinosis in the 1,000 mg/kg bw females. Small focal cortico-medullary

deposits of calcium were observed in 10 of the 16 high dose females while only 4/16 control females showed similar deposits. Proteinaceous casts were seen in the urinary bladders of 7 out of 16 1,000 mg/kg bw males versus only one in the control group. The casts were discussed to be originated by reflux of prostatic and seminal vesicle secretions. These observations are common findings in control rats of this strain. The toxicological significance of their increased incidences by ethyl acetoacetate treatment is unknown. Urinalysis revealed no indications of functional impairment of the kidney in treated animals.

Overall, it was concluded that the effects observed were treatment-related, but did not represent clearly ethyl acetoacetate-induced adverse effects. Therefore the NOAEL of this study was estimated to be 1,000 mg/kg bw/d.

No studies on repeated dose toxicity with other application routes are available.

No-observed-adverse-effect level (NOAEL): 1,000 mg/kg bw/d (Hazleton, 1991).

Human data:

No data available.

Conclusion:

No relevant toxic effects were seen in oral repeated dose studies in rats up to 1,000 mg/kg bw/d.

4.1.2.7 Mutagenicity

Bacterial studies

In a well conducted study ethyl acetoacetate did not induce gene mutations in bacteria in the absence or presence of Aroclor-induced rat liver S-9 mix in doses ranging from 4 to 10,000 µg/plate (Hoechst AG, 1988). The bacterial tester strains included Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538 and Escherichia coli WP2uvrA. There was no toxic effect.

Negative results were also obtained in a screening assay with Salmonella typhimurium strains TA92, TA94, TA98, TA100, TA1535 and TA1537 (Ishidate et al., 1984). In this investigation the pre-incubation methodology was used; doses up to 25,000 µg/plate were tested in presence of a Kanechlor-induced rat liver S-9 mix.

Mammalian cell studies

An in vitro chromosomal aberration test with V79 cells was negative with and without S-9 mix for doses ranging from 325 to 1301 µg/ml (Hoechst Marion Roussel, 1999). Treatment was for 3 h (with and without S-9 mix) and 20 h (only without S-9 mix); sampling was performed 20 h after start of the treatment. Clear inhibition of mitotic activity was observed after 20-h treatment without S-9 mix for doses of 650 and 1,301 µg/ml. The highest dose tested was equivalent to 10 mmol/l.

Also in a screening assay for induction of chromosomal aberration with CHL cells, ethyl acetoacetate did not induce an increase in aberrant cells when tested in doses of 500, 1,000 or 2,000 µg/ml without exogenous metabolic activation system (Ishidate, 1988). Cells were sampled 24 and 48 hours after start of treatment. This test is not fully reliable, since it was run only without S-9 mix and only 100 cells were analyzed per experimental point.

Conclusion

Ethyl acetoacetate is negative in a bacterial mutation test and in vitro chromosomal aberration tests. There is no concern with respect to mutagenicity. Ethyl acetoacetate should not be classified as a mutagen.

4.1.2.8 Carcinogenicity

No experimental data are available.

From experience on other comparable compounds in combination with the knowledge on the metabolites there is no reason to assume a concern regarding cancerogenic effects of the substance.

4.1.2.9 Toxicity for reproduction

Animal data

For ethyl acetoacetate a GLP conform Reproduction/Developmental Toxicity Screening Test according to OECD Guideline 421 had been performed (LPT, 1999, 2000). Groups of 10 rats (Sprague Dawley/CRL:CD®BR) per sex were treated with dosages of 0, 50, 225, and 1,000 mg/kg bw/day by gavage (administration volume 10 ml/kg bw/day) using tap water as vehicle for the control group. Males were treated daily from two weeks before mating until the end of the mating period. Females were treated daily from two weeks before mating until the 4th day of lactation.

Throughout the whole treatment period none of the low-, intermediate- and high-dosed male or female parent animals died. No substance-related behavioral changes were observed in the animals of either dose group. Body weight and body weight change was within the normal range of the control in males and females of the treated groups during all phases of the study. No substance-related influence was found on absolute and relative food consumption and on drinking water consumption compared to the control at the dosages of 50, 225, and 1,000 mg/kg bw/day.

In parent males no substance-related macroscopically visible changes were revealed at necropsy in any of the treated animals. Relative testes and epididymis weights of the treated males were within the range of the control group. Histopathological examination of these organs of males dosed with 1,000 mg/kg bw/day revealed no changes in any of the treated animals. Also in parent females no substance-related pathological findings had been revealed at necropsy. Histopathological examination of the ovaries of females dosed with 1,000 mg/kg bw/day did not give evidence for substance-related changes in any of the treated animals.

At the dose levels of 50 and 225 mg/kg bw/day no influence was noted on both the number of corpora lutea or implantations (see **Table 4.5**). In the high-dosed dams (1,000 mg/kg bw/day) the number of corpora lutea and implants was slightly decreased compared to the control, leading to a mean pre-implantation loss of 5.0% (concurrent control: 2.0%).

Pre-coital time was similar in both control animals and those of the treatment groups. Likewise, the duration of pregnancy of treated animals was within the range of the control and there was no influence on the parturition.

After birth, for the animals treated with 50 or 225 mg/kg bw/day there were no substance-related biological differences in comparison to the control group. The number of pups alive was not influenced, neither was sex distribution of the pups. Stillbirths or macroscopically visible malformed pups did not occur. The reproduction indices (birth index, live birth index, viability index) were not influenced and neither was maternal brood care.

At the dose level of 1,000 mg/kg bw/day the number of pups at birth and during the 4-day lactation period was slightly decreased compared to the control correlating with the reduced number of implants. Hence, the mean post-implantation loss was increased to 13.2% (concurrent control: 5.9%) and the mean birth index and live birth index (both: 86.8%) were decreased compared to the indices of the concurrent control (both: 94.1) (see **Table 4.5**). However, the mean viability index (97.6%) was in the range of the concurrent control (93.7%).

For all dose groups under investigation the body weights of pups on the 1st and the 4th lactation day was within the range of the control. At external observation on lactation day 4 pups did not reveal any substance-related pathological findings.

Taking into account the laboratory historical control data of 7 other OECD 421 studies (**cf. Table 4.5**), the effects observed in the current study after treatment with 1,000 mg ethyl acetoacetate/kg bw/day are not considered to be of toxicological significance. The extent of pre- and postimplantation loss and the decrease in mean litter birth /live birth indices fit within the ranges of the available historical control data. Thus, the effects observed at the highest dose level are not considered treatment-related.

No studies on reproductive toxicity with other application routes are available.

No-observed-adverse-effect level (NOAEL/reproductive toxicity): 1,000 mg/kg bw/day (LPT Report No. 11232/98).

For the risk assessment with respect to reproductive toxicity it has to be taken into consideration, that properties of ethyl acetoacetate to adversely affect reproduction could be evaluated only from an OECD 421 screening test (intrinsic limitations).

Human data

No data available.

Conclusion

There are no human data on the reproductive toxicity of ethyl acetoacetate.

The potential to adversely affect reproduction and development was investigated at a screening level during a study according to OECD Guideline 421 with the oral route of administration to rats.

No statistically significant effects were observed at doses up to and including 1,000 mg ethyl acetoacetate /kg bw/day taking into account the laboratory historical control data from 7 other OECD 421 studies. Hence, from the results of the current study a NOAEL for reproductive toxicity of 1,000 mg/kg bw/day can be estimated.

Table 4.5 Reproduction / Development Toxicity Study on Rats OECD Guideline 421

Parameter	Control	50 (mg/kg/ bw/d)	225 (mg/kg bw/d)	1000 (mg/kg bw/d)	Historical control	
					mean value ± SD (n = 7) *	range
Pre-implantation loss mean litter index in %	2.0	2.6	2.7	5.0	3.6 ± 1.8	1.4 – 6.9
Post-implantation loss mean litter index in %	5.9	6.3	5.4	13.2	8.1 ± 3.8	4.4 –13.8
Birth index mean litter index in %	94.1	93.7	94.7	86.8	91.2 ± 5.6	83.4 – 98.3
Live birth index mean litter index in %	94.1	93.7	94.7	86.8	90.6 ± 6.1	81.6 – 98.3

* Data were obtained from the control groups of 7 studies performed at LPT during 1997-2000 (LPT, 2000).

4.1.3 Risk characterisation

4.1.3.1 General aspects

Absorption of ethyl acetoacetate via the oral route is demonstrated in animals, absorption via the lungs can be assumed.

It may be anticipated that ethyl acetoacetate is partially cleaved already in the gastrointestinal tract due to acidic pH values or by bacterial activity. In a first metabolic step the absorbed portion of ethyl acetoacetate will be hydrolysed into 3-oxobutanoic acid and ethanol by the unspecific esterases of the blood. The acid moiety is an endogenous product within the lipid metabolism and is further metabolized predominantly to carbon dioxide and water; ethanol will be metabolized on known pathways.

For predicting in humans rates of ester hydrolysis using data derived from animal studies it has to be considered that in dependence on the prevailing substrate, esterase activities in human plasma are far lower than in rats as a rule. Therefore it is to anticipate, that the stability (half-life) of systemically available ethyl acetoacetate is clearly higher in humans than in rats.

The main route of elimination of ethyl acetoacetate and its metabolites is urinary excretion or exhalation of the metabolic product carbon dioxide in the breath.

Human data on acute toxicity and on local irritation caused by ethyl acetoacetate are not available. In animals, acute toxicity by the oral, dermal, and inhalative routes is low as judged by tests with rats. The substance demonstrated no or only mild skin irritation and mild eye irritation in tests with rabbits. Valid human or animal data on sensitization are not available.

Following repeated oral exposure of ethyl acetoacetate in rats, no treatment-related adverse effects (including haematology, clinical chemistry, gross necropsy and histopathology) were reported up to 1,000 mg/kg bw/d.

There is no information on health effects in humans following repeated exposure to ethyl acetoacetate via any route.

Ethyl acetoacetate is negative in a bacterial mutation test and in in vitro chromosomal aberration tests. There is no concern with respect to mutagenicity.

There are no data on cancerogenicity of ethyl acetoacetate. From experience on other comparable compounds in combination with the knowledge on the metabolites there is no reason to assume a concern regarding cancerogenic effects of the substance.

There are no human data on the reproductive toxicity of ethyl acetoacetate. The potential to adversely affect reproduction and development was investigated in rats at a screening level with the oral route of administration during a study according to OECD Guideline 421. No statistically significant effects were observed with doses up to and including 1,000 mg/kg bw/day. Moreover, taking into account the toxicological profile of ethyl acetoacetate, there is at present no concern for a potential to adversely affect reproduction.

4.1.3.2 Workers

4.1.3.2.1 Toxicological endpoints relevant for workplace risk assessment

Critical inhalation toxicity

Acute inhalation toxicity

Acute inhalation toxicity seems to be low as judged on the basis of a poorly reported test with rats surving an 8-hour exposure to saturated vapour (cf. Section 4.1.2.2). Because of a vapour pressure of ethyl acetoacetate of 1 hPa (20 °C), the theoretical saturation concentration is about 1,000 ml/m^3.

Repeated dose toxicity

Inhalation studies with repeated administration are not available. The systemic activity of ethyl acetoacetate is judged on the basis of the available oral 28-day studies in rats. In these studies, no toxic effects were observed at the highest tested oral dose of 1,000 mg/kg/d.

For human health risk assessment the experimental NOAEL of 1,000 mg/kg/d (rat, subacute, oral) has to be converted to the anticipated human NAEC for chronic inhalation exposure.

The chronic threshold level is assumed to be 1/6 of the experimental NOAEL of the subacute oral rat study. This default factor is derived from empirical data for various existing chemicals individually tested with different duration of exposure (BAU 1994).

Concerning route-to-route extrapolation the assumption is made that the amount of ethyl acetoacetate inhaled will lead to the same degree of systemic toxicity as does the same amount tested orally. Assuming a respiratory minute volume of the rat of 0.8 l/min/kg, duration of inhalation exposure of about 6 to 8 hours per day, deposition of substance inhaled is 100 % and respiratory tract absorption does not differ from oral absorption, for rats 1 mg/kg/d (orally) is toxicologically equivalent to about 3 mg/m^3 (route-to-route extrapolation factor for the rat for 6 hours is 3.5, for 8 hours is 2.6).

When extrapolating results from experimental animal bioassays to humans metabolic rate scaling is proposed provided the substance is acting systemically. The corresponding cross-species scaling factor for the inhalation route simply is 1 because laboratory animals and humans breathe at a rate depending on their metabolic rate.

Multiplication of the experimental NOAEL with the adjustment factors chosen ($1000 \cdot 1/6 \cdot 3 \cdot 1$) results in an anticipated human chronic NAEC of 500 mg/m^3 (approx. 100 ml/m^3). Intraspecies variability within the human population is not known.

There is a low degree of confidence in this predicted NAEC because of the uncertainties of route-to-route extrapolation, duration adjustment and intraspecies variability. It must be further kept in mind that the actual dose at which health effects would occur is not known; the actual oral NOAEL for the rat may be greater than, but not substantially higher than 1,000 mg/kg/d (because acute toxicity has been reported at dose levels of 2,000 – 4,000 mg/kg).

The extrapolation procedure used is to be considered as central tendency estimate; uncertainty factors have not been used. Thus extrapolation procedure chosen is not designed “to err on the side of safety”. Risk managers have to be fully aware of the characteristics of that extrapolation procedure.

Knowledge of the biotransformation of carboxylic esters leads to the assumption that a proportion of the inhaled ethyl acetoacetate will already be hydrolysed within the respiratory tract to acetoacetic acid and ethanol by carboxy-esterases. Acetoacetate is an endogenous product of accelerated fat metabolism. For ethanol there is a national occupational exposure limit of 1,000 ml/m^3. Provided that the ester is completely hydrolysed, no ethanol-related health damage is expected below 1,000 ml/m^3 ethyl acetoacetate.

For toxicological assessment of repeated inhalation exposure at the workplace, it is therefore assumed that the anticipated NAEC might lie between 100 ml/m^3 and 1,000 ml/m^3. The available knowledge on the toxicity of ethyl acetoacetate does not permit a more precise statement.

For reasons of comparability the NAEC without duration adjustment and metabolic rate scaling is calculated as well. The experimental NOAEL of 1,000 mg/kg/d (highest dose level tested) will correspond to a human NAEL of 70,000 mg/person/day. Assuming that a worker (70 kg) inhales 10 m^3 air per working day and that an adjustment factor for inhalatory uptake relative to oral uptake is not necessary, a NAEC of 7,000 mg/m^3 will result. This NAEC is 14 times the anticipated human chronic NAEC of 500 mg/m^3 (100 ppm, see above), the latter value being considered more relevant and used for risk assessment.

Reproductive toxicity

From an oral reproductive toxicity screening test (OECD 421) a NOAEL of 1,000 mg/kg/d is obtained. Taking into account historical control data, effects observed at the highest dose level of 1,000 mg/kg/d are not considered treatment-related. Thus, ethyl acetoacetate is not considered to be a reproductive toxicant. Risk assessment with respect to reproductive toxicity however should be aware of the intrinsic limitations of the OECD 421 screening test.

For risk assessment purposes at the workplace an air concentration in humans without reproductive toxic effect has to be derived from the oral NOAEL in rats. Species extrapolation is performed on the basis of metabolic rate scaling, resulting in an extrapolation factor of ¼ for transformation of oral rat data to humans. Calculation of an equipotent air concentration from the oral data simply uses bodyweight and respiratory volume of workers under the assumption, that there are no route-specific differences in reproductive toxicity for ethyl acetoacetate and the substance is similarly taken up by both routes. With this procedure the adjusted NAEC calculates to 1,750 mg/m^3 (1,000 mg/kg/day / 4 · 70 kg / 10 m^3). This value will be used in the following for risk assessment purposes concerning reproductive toxicity.

For reasons of comparability the direct NAEC without specific adjustment to humans is calculated as well. The experimental NOAEL of 1,000 mg/kg/d thus corresponds to 7,000 mg/m^3 (1,000 mg/kg/day x 70 kg / 10 m^3).

For better understanding of the text above it should be mentioned that the procedure to adjust data from animals to humans has continuously been modified as a consequence of the learning by doing process in risk assessment. The calculation outlined in the section *repeated dose toxicity*, which is a previous version of the developing extrapolation procedure, would therefore lead to a different result concerning the adjusted NAEC for reproductive toxicity. The calculation used now accounts for the fact that workers usually breath at a higher rate compared to the situation at rest. As a consequence the calculated air concentrations are lower compared to those which would have been obtained previously.

Critical dermal toxicity

Ethyl acetoacetate is not considered to be a local irritant. No studies have been performed with repeated dermal administration. Since no signs of toxicity were detected following repeated oral administration to rats even at the highest tested dose of 1,000 mg/kg/d, and acute dermal toxicity is still lower than acute oral toxicity, systemic toxicity of ethyl acetoacetate following repeated dermal exposure is likewise assumed to be negligibly small.

To get a quantitative estimate of the very low anticipated dermal toxicity it is assumed that dermal uptake might be 25 % of oral uptake (lowest LD_{50} oral: 3,980 mg/kg/d, LD_{50} dermal > 10,000 mg/kg/d). Because of the oral NOAEL of 1,000 mg/kg/d (highest dose level tested) the adjusted NOAEL for subacute dermal toxicity is calculated to be 4,000 mg/kg/d. Multiplication of 4,000 mg/kg/d with a human body weight of 70 kg yields a total dose of 280,000 mg/person/d. Taking account of duration adjustment (default factor 1/6) and metabolic rate scaling instead of body weight scaling (1/4) will decrease the total dose of 280,000 mg/person/day by a factor of 24 to the anticipated chronic human NAEL of > 12,000 (11,666) mg/person/day.

By an analoguous consideration the oral NOAEL for reproductive toxicity of 1,000 mg/kg/day can be converted in an anticipated dermal dose for human reproductive toxicity. With correction for dermal versus oral uptake and species extrapolation as outlined above a dermal NAEL adjusted to humans of approximately 70,000 mg/person (1,000 mg/kg/d · 4 · 70 kg / 4) is obtained.

4.1.3.2.2 Summary of effects relevant for workplace risk assessment

Table 4.6 Effects relevant for workplace risk assessment

	Inhalation	Dermal
Acute toxicity	No lethality at saturated vapour (8 h, 1 hPA (20 °C)) → 1,000 ml/m³ (rat)	LD_{50} > 10,000 mg/kg (rat)
Irritation/Corrosivity	Not considered to be a respiratory tract irritant	Not classified as 'irritating to skin or eyes'
Sensitization	No data; not suspected to be a respiratory sensitizer	Not suspected to be a skin sensitizer
Repeated dose toxicity (systemic)	Extrapolated NAEC > 100 ml/m³ (> 500 mg/m³) (highest dose level tested orally without adverse effects! (rat)	Extrapolated NAEL > 12,000 mg/person/day (highest dose level tested orally without adverse effects!)
Repeated dose toxicity (local)	Not considered to be a respiratory tract irritant	Not classified as 'irritating to skin or eyes'
Mutagenicity	Base set tests negative	
Carcinogenicity	No data; not suspected to be a carcinogene	
Fertility impairment/ developmental toxicity	Not considered to be a reproductive toxicant (screening study)	
	Adjusted NAEC = 1,750 mg/m³	Adjusted NAEL = 70,000 mg/person

4.1.3.2.3 Occupational risk assessment

For the purpose of risk characterisation, it is assumed that inhalation of vapour and skin exposure are the main routes of exposure. Oral exposure is not considered to be a significant route of exposure under normal working practices.

Acute toxicity

Inhalation

The acute inhalation toxicity in rats appears to be low. No lethality occurred at saturated vapour conditions with an estimated exposure concentration of 1,000 ml/m^3 (1 hPa, 20 °C). The highest exposure level reported is 13 ml/m^3 (68 mg/m^3) in the industrial area. This exposure lies far below 1,000 ml/m^3. During normal use acute inhalation risks are not considered of concern.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Dermal contact

The dermal LD_{50} for rats is > 10,000 mg/kg. This value is much higher than the calculated highest dermal exposure of 6 mg/kg (calculated on the basis of 1 mg/cm^2, exposed skin area 420 cm^2, 70 kg bodyweight). This level of exposure is calculated for the chemical industry and some industrial applications. Therefore acute dermal risks are not considered of concern.

Conclusion (ii)

Irritation/Corrosivity

Inhalation

Ethyl acetoacetate is not suspected to be a respiratory tract irritant. Inhalation exposure of workers is therefore not anticipated to result in relevant respiratory tract irritation.

Conclusion (ii)

Dermal contact

Ethyl acetoacetate is not classified as “irritating” to skin or eyes. Dermal contact at workplaces is therefore not anticipated to result in relevant local damage.

Conclusion (ii)

Sensitization

Inhalation

There are no data available on respiratory sensitization. For preliminary risk assessment ethyl acetoacetate is not suspected to be a respiratory sensitizer according to the fact, that during all the years of use no notice of specific case reports has been given. Thus inhalation exposure is not suspected to result in respiratory tract sensitization.

Conclusion (ii)

Dermal contact

According to 4.1.2.5, ethyl acetoacetate is not supposed to be a skin sensitizer. Dermal contact at workplaces is therefore not anticipated to result in skin sensitization.

Conclusion (ii)

Repeated-dose toxicity (systemic)

The relevant information (exposure, toxicity, MOS) is listed in **Table 4.7.**

Table 4.7 MOS values [repeated dose toxicity (systemic)] of ethyl acetoacetate

		Inhalation				Dermal contact				
Exposure scenario	Duration and frequency	Shift average value [mg/m³]	NAEC [mg/m³] extrap.	MOS (extrap.)	Con-clusion	Shift average value [mg/cm²/d]	Shift average value [mg/p/d]	NAEL [mg/p/d] extrap.	MOS (extrap.)	Con-clusion
Chemical industry										
Manufacturing (liquid) and further processing as a chemical intermediate (pharmaceuticals, pesticides, dyes and pigments), vapour (solution): drumming, transfer, cleaning, maintenance	shift length, daily	2.5	> 500	>200	ii	0.1 – 1[1]	42 - 420	> 12,000	> 29 - 286	ii
manufacture of cosmetics (especially nail varnish), vapour (solution): transfer, weighing, filling, drumming	shift length, daily	see above[2]	> 500	>200	ii	0.1 – 1[1]	42 - 420	> 12,000	> 29 - 286	ii
Industrial area										
use of perfume oils (content < 5 %) in the manufacture of cleaning products (content < 1 %) and air deodorants (< 1.25 %), vapour (solution): transfer, weighing, filling, drumming	batch processing 2 hours/daily	0.75 – 4[3] 14 – 68[4]	> 500 > 500	> 125 - 667 > 7 - 36	ii ii	0.005 - 0.05[1]	2 - 21	> 12,000	> 571-6,000	ii

Table 4.7 Continued overleaf

Table 4.7 Continued

		Inhalation				Dermal contact				
Exposure scenario	Duration and frequency	Shift average value [mg/m³]	NAEC [mg/m³] extrap.	MOS (extrap.)	Con-clusion	Shift average value [mg/cm²/d]	Shift average value [mg/p/d]	NAEL [mg/p/d] extrap.	MOS (extrap.)	Con-clusion
manufacture of polyester paints, use as an additive in resins and as hardening accelerator (formulation companies), vapour (solution): transfer, weighing, filling, drumming	batch processing 2 hours/daily	< 6[5] 0.75 – 4[3] 14 – 68[4]	> 500 > 500 > 500	> 83 > 125- 667 > 7 - 36	ii ii ii	0.1 – 1[1]	42 - 420	> 12,000	> 29 - 286	ii
manufacturing of foodstuffs and colour films together because of comparable standards of cleanliness, vapour (solution): transfer, weighing, filling, drumming	shift length, daily	3 – 16[6]	> 500	> 31 -167	ii	0.1 – 1[1]	42 - 420	> 12,000	> 29 - 286	ii
use as an additive in formulations, for impregnating and coating of paper, assumption: 5 %, vapour (solution): transfer, weighing, filling, mixing	shift length, daily	17.5[5] (90th-%)	> 500	> 29	ii	0.005 - 0.05[1]	2 - 21	> 12,000	> 571 – 6,000	ii
use as hardening accelerator in polyester paints during spray painting (content 1 - 5 %), vapour (solution): spray painting	shift length, daily	app. 20[5] 27 – 54[1]	> 500 > 500	> 25 > 9 - 18	ii ii	0.005 - 0.05[1]	6 - 65	> 12,000	> 185 – 2,000	ii

Table 4.7 Continued overleaf

Table 4.7 Continued

		Inhalation				Dermal contact				
Exposure scenario	Duration and frequency	Shift average value [mg/m³]	NAEC [mg/m³] extrap.	MOS (extrap.)	Con-clusion	Shift average value [mg/cm²/d]	Shift average value [mg/p/d]	NAEL [mg/p/d] extrap.	MOS (extrap.)	Con-clusion
Skilled trade										
use as hardening accelerator in polyester paints for repair lacquering during spray painting (content 1 - 5 %), vapour (solution): spray painting	only a few minutes frequency unknown; assumed: several times per day: 2 hours/daily	33.5 – 67[1]	> 500	> 7 - 15	ii	0.05 - 0.25[1]	65 - 325	> 12,000	> 37 - 185	ii
use of cleansers (all-purpose cleanser, washing detergents), content: 0.05 %, vapour (solution)	shorter than shift length, daily	0 - 0.6[1]	> 500	> 833	ii	0.0025 - 0.0075[1]	3 - 10	> 12,000	> 1 200 – 4,000	ii
use of cosmetics (nail-lacquers, after-shave lotion) content assumed 1 %, vapour (solution)	short-term, occasionally (nail-lacquers)	low[2]	> 500	very high	ii	low[2]	low	> 12,000	very high	ii
	short-term, daily (after-shave lotion)	low[2]	> 500	very high	ii	0.0125 - 0.0625[1]	5 - 26	> 12,000	> 461 - 2 400	ii

MOS (extrap.) relies upon NAEC resp. NAEL with modifications (metabolic rate scaling, duration adjustment).

ii There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already

1 EASE

2 expert judgement

3 EASE (with LEV), exposure shorter than shift length

4 EASE (without LEV), exposure shorter than shift length

5 comparison by analogy

6 EASE (with LEV)

Inhalation

Repeated inhalation toxicity data are not available. Based on subacute oral toxicity data a NAEC of > 500 mg/m^3 is extrapolated (see Section 4.1.3.2.1). The NAEC is considered to be greater than 500 mg/m^3 because the highest dose level tested orally was without adverse effects.

The NAEC is compared with the exposure information. For details see **Table 4.7**.

Prolonged inhalative exposure of ethyl acetoacetate is assumed for workplaces in the chemical industry (MOS 200) and in manufacturing of foodstuffs and colour films (MOS > 31 - 167), use in polyester paints (MOS > 25, > 9 - 18), use for impregnating and coating of paper (MOS > 29).

The exposure estimate in the chemical industry is based on measurement results, in the mentioned industrial applications on EASE calculations or on comparison by analogy.

With regard to the mentioned aspects systemic health risks due to chronic inhalation exposure are not expected.

Remark: For reasons of comparability it has to be mentioned that the direct MOS without duration adjustment and without metabolic rate scaling is 14 times the adjusted MOS.

Conclusion (ii)

Dermal contact

Because there are no repeated dermal toxicity data, a NAEL of > 12,000 mg/p/d was calculated using test results from a subacute oral toxicity study. Again it has to be mentioned that there were no adverse effects at the highest dose level tested orally.

The NAEL is compared with the exposure information. For details see **Table 4.7.**

Assuming the highest level of the estimation according to EASE for the unprotected worker in industry as a worst case repeated dermal exposure of 420 mg/p/d (highest level in industry, without PPE) the calculated MOS would be > 29.

Systemic health risks due to repeated dermal exposure are not expected.

Remark: For reasons of comparability it has to be mentioned that the direct MOS without duration adjustment and without metabolic rate scaling is 24 times the adjusted MOS.

Conclusion (ii)

Combined exposure (inhalation, dermal contact)

Systemic health effects due to combined exposure (inhalation and skin contact) are to be assessed in addition to route-specific risk estimates. The most critical MOS for inhalation exposure was calculated to be greater than 7, the most critical MOS for skin contact greater than 29. The specific relation of these route-specific MOS-values shows that systemic dermal risks in relation to systemic inhalation risks are of minor importance, thus calculated dermal risks do not substantially contribute to the overall risk due to combined exposure.

The MOS value of 7 for inhalation implies that inhalation exposure is 14 % of the NAEC, likewise the MOS of 29 for skin contact implies that dermal exposure is 3 % of the corresponding NAEL. Thus combined exposure amounts to 17 % of the anticipated no adverse effect level. This combined percentage of 17 % is equivalent to the MOS for combined exposure

of about 6 (100/17). The MOS for combined exposure of 6 is only insignificantly smaller than the most critical route-specific MOS for inhalation of 7.

Thus systemic health risks due to combined exposure are not considered of concern.

Conclusion (ii)

Repeated-dose toxicity (local)

Inhalation

Ethyl acetoacetate is not considered to be a respiratory tract irritant. Repeated inhalation exposure of workers is not anticipated to result in relevant respiratory tract irritation.

Conclusion (ii)

Dermal contact

Ethyl acetoacetate is not classified as 'irritating' to skin or eyes. Acute dermal contact at workplaces is not anticipated to result in relevant local damage. Although data are not sufficient to allow a definite assessment of chronic local effects, repeated dermal contact to a substance not classified as an irritant is considered to justify the conclusion of no concern.

Conclusion (ii)

Mutagenicity

According to negative base set tests there is no concern for ethyl acetoacetate with respect to mutagenicity. Therefore risks at workplace are not to be expected.

Conclusion (ii)

Carcinogenicity

There are no carcinogenicity data available. Ethyl acetoacetate is not suspected to be a carcinogen. Relating to this toxicological endpoint ethyl acetoacetate exposure is not considered of concern.

Conclusion (ii)

Reproductive toxicity

Inhalation

In an oral reproductive toxicity screening study (OECD 421) ethyl acetoacetate did not prove to be a reproductive toxicant. Against the background of historical control data effects observed at 1,000 mg/kg/d (the highest dose level tested) are not considered treatment-related; thus a NOAEL of 1,000 mg/kg/d is obtained. With reference to chapter 4.1.3.2.1, an adjusted NAEC of 1,750 mg/m³ is used for worker risk assessment.

The highest shift average value is reported to be 68 mg/m³ (industrial area and skilled trade; compare **Table 4.7**). Based on the adjusted NAEC of 1,750 mg/m³ a lowest adjusted MOS of 26 is calculated. Without adjustment (here factor 4 for metabolic rate scaling) the lowest direct MOS for reproductive toxicity is 104. Evaluation of these MOS values have to take into account that the assessment of reproduction toxicity is based on a screening test with its intrinsic statistical limitations and that the establishment of the NOAEL at the highest dose level tested

required the comparison of test results with historical control groups. However, emphasizing that the results of the screening study did not show treatment-related embryotoxicity, conclusion ii seems to be appropriate for all exposure scenarios. Nevertheless, based on available screening data, possible toxicological consequences due to exposure levels higher than reported cannot be assessed with sufficient certainty.

Conclusion (ii)

Dermal contact

For dermal contact an adjusted NAEL concerning reproductive toxicity was calculated to lie at about 70,000 mg/person (see Section 4.1.3.2.1). Compared with the highest dermal shift average value of 420 mg/person a lowest adjusted MOS value of 167 is obtained. Without adjustment (here a factor of 4 for metabolic rate scaling) a lowest direct MOS of 668 is obtained. Taking into account that a potential of reproductive toxicity could not be ascertained, these lowest MOS values are not considered to be of concern.

Conclusion (ii)

4.1.3.2.4 Overall conclusions for worker risk assessment

The conclusions for occupational risk assessment are summarized in the following table. Irrespective of conclusion ii for workers for all exposure scenarios and toxicological endpoints information should be given that health effects (namely reproductive toxicity) at exposure levels exceeding those documented in the report cannot be assessed with sufficient certainty.

Table 4.8 Conclusions of the occupational risk assessment

Toxicological endpoints	All exposure scenarios
Acute toxicity	ii
Irritation/Corrosivity	ii
Sensitization	ii
Repeated dose toxicity	ii
Mutagenicity	ii
Carcinogenicity	ii
Toxicity for reproduction	ii

Conclusion (ii): There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

4.1.3.3 Consumers

Acute Toxicity

Human data on acute toxicity are not available.

Acute toxicity by the oral, dermal, and inhalative routes is low as judged by tests with rats: oral LD50 values of 3,980 mg/kg bw and higher are reported; the dermal LD50 is higher than 10,300 mg/kg bw; after eight hours of exposure, saturated substance vapours caused no deaths in rats.

Irritation

Human data on irritation caused by ethyl acetoacetate are not available. Ethyl acetoacetate has demonstrated no or only mild irritating properties to the skin of rabbits, depending on the duration of exposure and the dose. The substance is mildly irritating to the eyes of rabbits.

Corrosivity

Ethyl acetoacetate has no corrosive properties.

Conclusion for acute toxicity, irritation and corrosivity

Based on the submitted data, ethyl acetoacetate is not to be classified according to EU regulations

Conclusion (**ii)** There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Sensitization

Consumer exposure may occur as a result of using cosmetics and household products. Valid human or animal data on sensitization properties of ethyl acetoacetate are not available.

Conclusion (**ii)** There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Taking into account the long experience with human exposure to the substance and the absence of any reports on contact allergy in exposed persons, there are no indications that ethyl acetoacetate may exhibit skin sensitizing properties.

Repeated dose toxicity

Consumer exposure may occur as a result of using cosmetics and household products. The combined exposure to the odorant in these products amounts to a predicted exposure in the upper µg range/kg bw/day.

Two studies in rats have shown that no relevant treatment-related effects occurred associated with repeated oral administration. The highest dose tested was 1,000 mg/kg bw/d.

For the decision on the appropriateness of MOS, the following aspects have been considered and taken into account:

Overall confidence in the database

The data taken into account for performing the risk characterization have been evaluated with regard to their reliability, relevance and completeness according to section 3.2 of the TGD. The data were submitted to the Competent Authority in two private reports. One report was adequately detailed and in accordance with internationally recognized guidelines and to GLP, the other one suffered from lack of certain data (see Section 4.1.2.6) but was published in a peer reviewed journal.

The findings of the studies are not contradictory so that the judgment can be based on the database. There are no reasons to assume limited confidence on the data being the basis of the risk characterization.

Uncertainty arising from the variability in the experimental data

The studies cited above allow to conclude that no treatment-related microscopic and macroscopic findings were observed up to the highest dose tested (1,000 mg/kg bw/d). Results of both studies were in conformity. There are no reasons to assume a special extent of uncertainty which have to be taken into account.

Intra- and interspecies variation

Data on kinetics of the substance are limited and do not allow to calculate the intraspecies and interspecies variability by applying modern approaches. Concerning hydrolysis of the substance, however, and for predicting in humans rates of ester hydrolysis using data derived from animal studies one has to consider that esterase activities in human plasma are generally lower than those p.e. in the rat. This conclusion is based on species differences in hydrolysis of different substances such as ester-type drugs and prodrugs. Therefore it has to be assumed, that the stability (half-life) of systemically available ethyl acetoacetate is clearly higher in humans than in rats.

This concern has to be considered and may be expressed in the magnitude of the MOS.

Nature and severity of the effect

There are no treatment-related effects reported. There are no reasons to assume that the effects shown in the animal experiments are limited to the species tested, thus being not of relevance for humans. Therefore there is no reason to assume concern which has to be expressed in an increased MOS.

Dose response relationship

There are no treatment-related effects reported up to the highest dose tested (1,000 mg/kg bw/d). Therefore there is no reason to assume concern which has to be expressed in an increased MOS taking into account the exposure level.

Differences in exposure (route, duration, frequency and pattern)

The estimated total chronic body burden with an assumed absorption of 100% is compared with the highest dose tested in an oral study (NOAEL) of 28 day-duration.

There are no reasons to assume that special concern can be derived neither from this procedure nor from the available toxicokinetic information; concerning different routes inasmuch as absorption was set with 100%.

Human population to which the quantitative and/or qualitative information on exposure applies

Following the exposure scenario there is no reason to assume a special risk for elderly, children or other people suffering from special diseases like obesity or persons with high bronchial reactivity.

Other factors

There are no other factors known requiring a peculiar margin of safety.

MOS for combined inhalation and dermal exposure scenario

The total predicted internal dose following inhalatory and dermal exposure is <1 mg/kg bw/d. The margin of safety between the

estimated exposure level of <1 mg/kg bw/d
and the
oral NOAEL of 1,000 mg/kg bw/d

is judged to be sufficient, even if the special consideration on interspecies variation is taken into consideration.

Conclusion for repeated dose toxicity

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Mutagenicity

Ethyl acetoacetate was negative in bacterial mutation assays as well as in a chromosomal aberration assay performed with and without metabolic activation.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Cancerogenicity

There are no data on the cancerogenicity of ethyl acetoacetate. From experience on other comparable compounds in combination with the knowledge on the metabolites there is no reason to assume a concern regarding cancerogenic effects of the substance.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Reproductive toxicity

Following the exposure assessment consumers may be exposed to ethyl acetoacetate via inhalation and/or dermal routes. The combined exposure to the odorant in cosmetics and household products is predicted to be in the upper µg range/kg bw/day.

Data from a screening study according to OECD Guideline 421 with oral administration to rats did not give evidence for adverse effects up to 1000 mg/kg bw/day. A NOAEL for reproductive toxicity of 1,000 mg/kg bw/day was estimated (cf. Section 4.1.2.9).

For the decision on the appropriateness of MOS, the following aspects regarding the critical effect as well as exposure have been considered and taken into account:

Overall confidence in the database

The data taken into account for performing the risk characterization have been evaluated with regard to their reliability, relevance and completeness according to section 3.2 of the TGD. The data were submitted to the Competent Authority in a private report being adequately detailed and in accordance with internationally recognized guidelines and to GLP (cf. Section 4.1.2.9).

There are no reasons to assume limited confidence.

Uncertainty arising from the variability in the experimental data

No special concerns have to be raised from this point.

Intra- and interspecies variation

There are no indication to limit the findings to a single species.

Nature and severity of the effect

Certain influences on reproduction have been observed after treatment with 1000 mg/kg bw (cf. Section 4.1.2.9). However, the findings fit within the ranges of the historical control data. Thus, the effects observed at the highest dose level are not considered treatment-related.

Dose-response-relationship

The mentioned effects were observed at high doses.

There is reason to assume some concern which has to be expressed in an increased MOS taking into account the exposure level.

Differences in exposure (route, duration, frequency and pattern)

Following the exposure assessment, the consumer may be exposed to ethyl acetoacetate via inhalation and dermal exposures. The estimated body burden with an assumed absorption of 100% is compared with an oral NOAEL from a Screening study according OECD Guideline 421.

There are no reasons to assume that special concern can be derived neither from this procedure nor from the available toxicokinetic information concerning different routes inasmuch as absorption was set with 100%.

MOS for combined inhalation and dermal exposure

The total predicted inhalation and dermal exposure is <1 mg/kg bw/d. The margin of safety between the

estimated exposure level of < 1 mg/kg bw/d

and the

oral NOAEL of 1000 mg/kg bw/d

is judged to be sufficient, even if it is taken into account that properties of ethyl acetoacetate to adversely affect reproduction could be evaluated only from an OECD 421 screening test.

Conclusion for reproductive toxicity

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

4.1.3.4 Humans exposed via the environment

Indirect exposure via the environment is calculated using data for intake via drinking water, food and air. An intake of a total daily dose of 0.787 µg/kg bw is calculated for the local scenario and 0.00141 µg/kg bw for the regional scenario.

In the repeated dose toxicity study in rats (28-day, oral) the NOAEL was 1,000 mg/kg bw/d.

From the results of an OECD-Guideline 421 study with oral application to rats a NOAEL for reproductive toxicity of 1,000 mg/kg bw/d was estimated.

The ratio expected exposure/NOAEL for Repeated Dose Toxicity and Reproductive Toxicity is very low and the resulting margins of safety are considered to be sufficient. The substance is of no concern in relation to indirect exposure via the environment.

Conclusion (**ii)** There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

In view of its chemical structure, ethyl acetoacetate is not expected to have an oxidizing potential. The substance is neither explosive nor flammable. Therefore with regard to the physico-chemical properties and with regard to the occupational exposure (described in Section 4.1.1.2) and the consumer exposure (described in Section 4.1.1.3) ethyl acetoacetate is not expected to cause specific concern relevant to human health.

Conclusion (**ii)** There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

5 CONCLUSIONS / RESULTS

5.1 ENVIRONMENT

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

5.2.1.1 Workers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Irrespective of conclusion ii for workers for all exposure scenarios and toxicological endpoints information should be given that health effects at exposure levels exceeding those documented in the report cannot be assessed with sufficient certainty.

5.2.1.2 Consumers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

5.2.1.3 Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

5.2.2 Human health (risks from physico-chemical properties)

Given the physico-chemical data, ethyl acetoacetate is considered not to form a risk with respect to flammability, explosive properties, and oxidising properties (**conclusion ii**).

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

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ABBREVIATIONS

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
bw	body weight / *Bw*, *b.w.*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 50 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]

EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 t/a)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient

Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration

pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst Case
S phrases	Safety phrases according to Annex III of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document [1]
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum

UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)

Appendix 1 Distribution and Fate

Substance:	AEEE (CAS: 141-97-9)
melting point: (sublimation)	$MP := -42 \cdot K$
vapour pressure:	$VP := 100 \cdot Pa$
water solubility:	$SOL := 125000 \cdot mg \cdot l^{-1}$
part. coefficient octanol/water:	$LOGP_{OW} := 0.25$
molecular weight:	$MOLW := 0.13 \cdot kg \cdot mol^{-1}$
gas constant:	$R := 8.314 \cdot J \cdot mol^{-1} \cdot K^{-1}$
temperature:	$T := 293 \cdot K$
conc. of suspended matter in the river:	$SUSP_{water} := 15 \cdot mg \cdot l^{-1}$
density of the solid phase:	$RHO_{solid} := 2500 \cdot kg \cdot m^{-3}$
volume fraction water in susp. matter:	$Fwater_{susp} := 0.9$
volume fraction solids in susp.matter:	$Fsolid_{susp} := 0.1$
volume fraction of water in sediment:	$Fwater_{sed} := 0.8$
volume fraction of solids in sediment:	$Fsolid_{sed} := 0.2$
volume fraction of air in soil:	$Fair_{soil} := 0.2$
volume fraction of water in soil:	$Fwater_{soil} := 0.2$
volume fraction of solids in soil:	$Fsolid_{soil} := 0.6$
aerobic fraction of the sediment comp.:	$Faer_{sed} := 0.1$
product of CONjunge and $SURF_{air}$:	$product := 10^{-4} \cdot Pa$

distribution air/water: Henry-constant

$$HENRY := \frac{VP \cdot MOLW}{SOL} \qquad HENRY = 0.104 \circ Pa \cdot m^3 \cdot mol^{-1}$$

$$\log\left(\frac{HENRY}{Pa \cdot m^3 \cdot mol^{-1}}\right) = -0.983 \qquad HENRY = 1.0264 \cdot 10^{-6} \circ atm \cdot m^3 \cdot mol^{-1}$$

$$K_{air\_water} := \frac{HENRY}{R \cdot T} \qquad K_{air\_water} = 4.26929 \cdot 10^{-5}$$

solid/water-partition coefficient Kp_{comp} and total compartment/water-partition coefficient K_{comp_water}

$a := 0.52$ (a,b from TGD, p. 539, table 4 "Nonhydrophobics")

$b := 1.02$

$K_{OC} := 10^{a \cdot LOGP_{OW} + b} \cdot l \cdot kg^{-1}$

$K_{OC} = 14.13 \, l \cdot kg^{-1}$ $\log\left(\frac{K_{OC}}{l \cdot kg^{-1}}\right) = 1.15$

Suspended matter

$Kp_{susp} := 0.1 \cdot K_{OC}$ $Kp_{susp} = 1.413 \, l \cdot kg^{-1}$

$K_{susp\_water} := Fwater_{susp} + Fsolid_{susp} \cdot Kp_{susp} \cdot RHO_{solid}$ $K_{susp\_water} = 1.253$

factor for the calculation of $Clocal_{water}$:

$faktor := 1 + Kp_{susp} \cdot SUSP_{water}$ $faktor := 1$

Sediment

$Kp_{sed} := 0.05 \cdot K_{OC}$ $Kp_{sed} = 0.706 \, l \cdot kg^{-1}$

$K_{sed\_water} := Fwater_{sed} + Fsolid_{sed} \cdot Kp_{sed} \cdot RHO_{solid}$ $K_{sed\_water} = 1.1531$

Soil

$Kp_{soil} := 0.02 \cdot K_{OC}$ $Kp_{soil} = 0.283 \, l \cdot kg^{-1}$

$K_{soil\_water} := Fair_{soil} \cdot K_{air\_water} + Fwater_{soil} + Fsolid_{soil} \cdot Kp_{soil} \cdot RHO_{solid}$

$K_{soil\_water} = 0.6238$

Sludge (activated sludge)

$K_{p\_sludge} := 0.37 \cdot K_{OC}$ $K_{p\_sludge} = 5.2264 \, l \cdot kg^{-1}$

Elimination in STPs

rate constant in STP: k = 1 h^{-1}

elimination P = f (k, logPow, logH) = 91%

fraction directed to surface water $Fstp_{water}$ = 9%

biodegradation in different compartments

surface water

$kbio_{water} := 4.7 \cdot 10^{-2} \cdot d^{-1}$ (TGD, p. 283, table 5)

soil

$DT50bio_{soil} := 30 \cdot d$ (TGD, p. 284, table 6)

$kbio_{soil} := \frac{\ln(2)}{DT50bio_{soil}}$ $kbio_{soil} = 0.023 \cdot d^{-1}$

sediment

$kbio_{sed} := \frac{\ln(2)}{DT50bio_{soil}} \cdot Faer_{sed}$ $kbio_{sed} = 2.31 \cdot 10^{-3} \cdot d^{-1}$

degradation in surface waters

$khydr_{water} := 4.655 \cdot 10^{-3} \cdot d^{-1}$

$kphoto_{water} := 1 \cdot 10^{-99} \cdot d^{-1}$

$kbio_{water} = 0.047 \cdot d^{-1}$

$kdeg_{water} := kphoto_{water} + kbio_{water} + khydr_{water}$

$kdeg_{water} = 0.052 \cdot d^{-1}$

Atmosphere

calculation of CONjunge * SURFaer for the OPS-model

$Fass_{aer} := \frac{product}{VP + product}$ $Fass_{aer} = 1 \cdot 10^{-6}$

degradation in the atmosphere

$kdeg_{air} := 2.8 \cdot 10^{-3}\ h^{-1}$ (see AOP – calculation)

Appendix 2 Indirect exposure

Definitions (for the use in this document)

definition of the unit 'kg$_{bw}$' for body weight	$kg_{bw} := 1 \cdot kg$
definition of the unit 'd' for day	$d := 1 \cdot Tag$
	$scenario := 1..2$
	$local := 1$
	$regional := 2$

Constants

gas - constant R	$R := 8.314 J \cdot K^{-1} \cdot mol^{-1}$

Defaults

volumefraction air in plant tissue [-]	$Fair_{plant} := 0.3$
volumefraction water in plant tissue [-]	$Fwater_{plant} := 0.65$
volumefraction lipids in plant tissue [-]	$Flipid_{plant} := 0.01$
bulk density of plant tissue [$kg_{wet\ plant} * m_{plant}^{-3}$]	$RHO_{plant} := 700 \cdot kg \cdot m$
leaf surface area [m^2]	$AREA_{plant} := 5 \cdot m^2$
conductance (0.001 m*s^{-1}) [m*d^{-1}]	$g_{plant} := 0.001 \cdot m \cdot s^{-1}$
shoot volume [m^3]	$V_{leaf} := 0.002 \cdot m^3$
transpiration stream [m^3*d^{-1}]	$Q_{transp} := 1 \cdot 10^{-3} \cdot m^3 \cdot$
correction exponent for differences between plant lipids and octanol [-]	$b := 0.95$
growth rate constant for dilution by growth [d^{-1}]	$kgrowth_{plant} := 0.035$
pseudo-first order rate constant for metabolism in plants [d^{-1}]	$kmetab_{plant} := 0 \cdot d^{-1}$
pseudo-first order rate constant for photolysis in plants [d^{-1}]	$kphoto_{plant} := 0 \cdot d^{-1}$

concentration in meat and milk

daily intake of grass
[$kg_{wet\,grass}$*d^{-1}]

$IC_{grass} := 67.6 \cdot kg \cdot d^{-1}$

daily intake of soil
[$kg_{wet\,soil}$*d^{-1}]

$IC_{soil} := 0.46 \cdot kg \cdot d^{-1}$

daily intake of air
[m_{air}^3*d^{-1}]

$IC_{air} := 122 \cdot m^3 \cdot d^{-1}$

daily intake of drinkingwater
[l*d^{-1}]

$IC_{drw} := 55 \cdot l \cdot d^{-1}$

daily intake for human

daily intake for the several pathways
[kg_{chem}*d^{-1}] or [m^3*d^{-1}]

$IH_{drw} := 2 \cdot l \cdot d^{-1}$

$IH_{fish} := 0.115 \cdot kg \cdot d^{-1}$

$IH_{stem} := 1.2 \cdot kg \cdot d^{-1}$

$IH_{root} := 0.384 \cdot kg \cdot d^{-1}$

$IH_{meat} := 0.301 \cdot kg \cdot d^{-1}$

$IH_{milk} := 0.561 \cdot kg \cdot d^{-1}$

$IH_{air} := 20 \cdot m^3 \cdot d^{-1}$

bioavailability through route of intake
[-]

$BIO_{inh} := 0.75$

$BIO_{oral} := 1.0$

average body weight of human
[kg]

$BW := 70 \cdot kg_{bw}$

Name: AEEE formulation 5/36 CAS - No.:141-97-9

Input

chemical properties

octanol-water partitioning coefficient [-]	$logK_{OW} := 0.25$ $K_{OW} := 10^{logK_{OW}}$
Henry - partitioning coefficient [Pa*m^3*mol^{-1}]	$HENRY := 0.1 \cdot Pa \cdot m^3 \cdot mol^{-1}$
air-water partitioning coefficient [-]	$K_{air\_water} := 4.27 \cdot 10^{-5}$
fraction of the chemical associated with aerosol particles [-]	$F_{ass\_aer} := 1 \cdot 10^{-6}$
half-life for biodegration in surface water [d]	$DT_{50\_bio\_water} := 15 \cdot d$

environmental concentrations

annual average local PEC in surface water (dissolved) [mg$_{chem}$ * l$_{water}^{-1}$]	$PEClocal_{water\_ann} := 0.022 \cdot mg \cdot l^{-1}$
annual average local PEC in air (total) [mg$_{chem}$ * m$_{air}^{-3}$]	$PEClocal_{air\_ann} := 2.448 \cdot 10^{-4} \cdot mg \cdot m^{-3}$
local PEC in grassland (total), averaged over 180 days [mg$_{chem}$ * kg$_{soil}^{-1}$]	$PEClocal_{grassland} := 6.681 \cdot 10^{-5} \cdot mg \cdot kg^{-1}$
local PEC in porewater of agriculture soil [mg$_{chem}$ * l$_{porewater}^{-1}$]	$PEClocal_{agr\_soil\_porew} := 1.075 \cdot 10^{-4} \cdot mg \cdot l^{-1}$
local PEC in porewater of grassland [mg$_{chem}$ * l$_{porewater}^{-1}$]	$PEClocal_{grassland\_porew} := 1.82 \cdot 10^{-4} \cdot mg \cdot l^{-1}$
local PEC in groundwater under agriculture soil [mg$_{chem}$ * l$_{water}^{-1}$]	$PEClocal_{grw} := 1.075 \cdot 10^{-4} \cdot mg \cdot l^{-1}$
regional PEC in surface water (dissolved) [mg$_{chem}$ * l$_{water}^{-1}$]	$PECregional_{water} := 4.0 \cdot 10^{-5} \cdot mg \cdot l^{-1}$
regional PEC in air (total) [mg$_{chem}$ * m$_{air}^{-3}$]	$PECregional_{air} := 3.7 \cdot 10^{-7} \cdot mg \cdot m^{-3}$
regional PEC in agriculture soil (total) [mg$_{chem}$*kg$_{soil}^{-1}$	$PECregional_{agr\_soil} := 1.8 \cdot 10^{-6} \cdot mg \cdot kg^{-1}$
regional PEC in porewater of agriculture soils [mg$_{chem}$*l$_{water}^{-1}$	$PECregional_{agr\_soil\_porew} := 5.0 \cdot 10^{-6} \cdot mg \cdot l^{-1}$

Definition of the concentrations used for indirect exposure

$C_{water_{local}} := PEClocal_{water\_ann}$

$C_{air_{local}} := PEClocal_{air\_ann}$

$C_{grassland_{local}} := PEClocal_{grassland}$

$C_{agr\_porew_{local}} := PEClocal_{agr\_soil\_porew}$

$C_{grass\_porew_{local}} := PEClocal_{grassland\_porew}$

$C_{grw_{local}} := PEClocal_{grw}$

$C_{water_{regional}} := PECregional_{water}$

$C_{air_{regional}} := PECregional_{air}$

$C_{grassland_{regional}} := PECregional_{agr\_soil}$

$C_{agr\_porew_{regional}} := PECregional_{agr\_soil\_porew}$

$C_{grass\_porew_{regional}} := PECregional_{agr\_soil\_porew}$

$C_{grw_{regional}} := PECregional_{agr\_soil\_porew}$

<u>bioconcentration in fish</u>

bioconcentration factor for fish
[$m_{water}^3 * kg_{chem}^{-1}$]

$$BCF_{fish} := 10^{0.85 \cdot \log K_{OW} - 0.7} \cdot l \cdot kg^{-1}$$

modified equation for logKow > 6

$$BCF_{fish} := wenn\left[\log K_{OW} > 6, \left[-0.278 \cdot \left(\log K_{OW}\right)^2 + 3.38 \cdot \log K_{OW} - 5.94\right] \cdot l \cdot kg^{-1}, BCF_{fish}\right]$$

$$C_{fish_{scenario}} := BCF_{fish} \cdot C_{water_{scenario}}$$

<u>bioconcentration in plants</u>

$$K_{plant\_water} := Fwater_{plant} + Flipid_{plant} \cdot K_{OW}^{b}$$

$$Croot_{agr\_plant_{scenario}} := \frac{K_{plant\_water} \cdot C_{agr\_porew_{scenario}}}{RHO_{plant}}$$

$$TSCF := 0.784 \cdot e^{\frac{-\left(\log K_{OW} - 1.78\right)^2}{2.44}}$$

remark: for $\log K_{OW}$ out of the range from -0.5 to 4.5
the TSCF is limited by the values for $\log K_{OW}$ = -0.5 resp. 4.5

$$TSCF := wenn\left(\log K_{OW} < -0.5, 0.903, TSCF\right)$$

$$TSCF := wenn\left(\log K_{OW} > 4.5, 0.832, TSCF\right)$$

$$K_{leaf\_air} := Fair_{plant} + \frac{K_{plant\_water}}{K_{air\_water}}$$

$$kelim_{plant} := kmetab_{plant} + kphoto_{plant}$$

$$\alpha := \frac{AREA_{plant} \cdot g_{plant}}{K_{leaf\_air} \cdot V_{leaf}} + kelim_{plant} + kgrowth_{plant}$$

$$\beta_{agr\_plant_{scenario}} := C_{agr\_porew_{scenario}} \cdot TSCF \cdot \frac{Q_{transp}}{V_{leaf}} + \left(1 - F_{ass\_aer}\right) \cdot C_{air_{scenario}} \cdot g_{plant} \cdot \frac{AREA_{plant}}{V_{leaf}}$$

$$C_{leaf\_crops_{scenario}} := \frac{\beta_{agr\_plant_{scenario}}}{\alpha \cdot RHO_{plant}}$$

$$\beta_{grass\_plant_{scenario}} := C_{grass\_porew_{scenario}} \cdot TSCF \cdot \frac{Q_{transp}}{V_{leaf}} + \left(1 - F_{ass\_aer}\right) \cdot C_{air_{scenario}} \cdot g_{plant} \cdot \frac{AREA_{plant}}{V_{leaf}}$$

$$C_{leaf\_grass_{scenario}} := \frac{\beta_{grass\_plant_{scenario}}}{\alpha \cdot RHO_{plant}}$$

purification of drinking water

system may defined dependent from the aerobic biodegradation

$$system := wenn\left(DT_{50\_bio\_water} < 10 \cdot d, 0, 1\right)$$

select a column on dependence from log K_{OW}

$$FIndex := if\left(logK_{OW} < 4, 0, wenn\left(logK_{OW} > 5, 2, 1\right)\right)$$

$$Fpur_{logKow} := \begin{bmatrix} 1 & \frac{1}{4} & \frac{1}{16} \\ 1 & \frac{1}{2} & \frac{1}{4} \end{bmatrix}$$

$$Fpur := \frac{Fpur_{logKow_{system, FIndex}}}{wenn\left(HENRY > 100 \cdot Pa \cdot m^3 \cdot mol^{-1}, 2, 1\right)}$$

$$C_{drw_{scenario}} := wenn\left[C_{grw_{scenario}} > \left(C_{water_{scenario}} \cdot Fpur\right), C_{grw_{scenario}}, C_{water_{scenario}} \cdot Fpur\right]$$

Biotransfer to meat and milk

$$BTF_{meat} := 10^{-7.6 + logK_{OW}} \cdot kg^{-1} \cdot d$$

remark: for $logK_{OW}$ out of the range from 1.5 to 6.5
the BTF_{meat} is limited by the values for $logK_{OW}$ = 1.5 resp. 6.5

$$BTF_{meat} := wenn\left(logK_{OW} < 1.5, 7.943 \cdot 10^{-7} \cdot kg^{-1} \cdot d, BTF_{meat}\right)$$

$$BTF_{meat} := wenn\left(logK_{OW} > 6.5, 0.07943 kg^{-1} \cdot d, BTF_{meat}\right)$$

$$C_{meat_{scenario}} := BTF_{meat} \cdot \left(\begin{array}{l} C_{leaf\_grass_{scenario}} \cdot IC_{grass} + C_{grassland_{scenario}} \cdot IC_{soil} \cdots \\ + C_{air_{scenario}} \cdot IC_{air} + C_{drw_{scenario}} \cdot IC_{drw} \end{array} \right)$$

$$BTF_{milk} := 10^{-8.1 + logK_{OW}} \cdot kg^{-1} \cdot d$$

remark: for $logK_{OW}$ out of the range from 3 to 6.5
the BTF_{milk} is limited by the values for $logK_{OW}$ = 1.5 resp. 6.5

$$BTF_{milk} := wenn\left(logK_{OW} < 3, 7.943 \cdot 10^{-6} \cdot kg^{-1} \cdot d, BTF_{milk}\right)$$

$$BTF_{milk} := wenn\left(logK_{OW} > 6.5, 0.02512 \cdot kg^{-1} \cdot d, BTF_{milk}\right)$$

$$C_{milk_{scenario}} := BTF_{milk} \cdot \left(\begin{array}{l} C_{leaf\_grass_{scenario}} \cdot IC_{grass} + C_{grassland_{scenario}} \cdot IC_{soil} \cdots \\ + C_{air_{scenario}} \cdot IC_{air} + C_{drw_{scenario}} \cdot IC_{drw} \end{array} \right)$$

total daily intake for human

daily dose through intake of several pathways
[$kg_{chem}*kg_{bw}^{-1}*d^{-1}$]

$$DOSE_{drw_{scenario}} := \frac{C_{drw_{scenario}} \cdot IH_{drw}}{BW} \qquad DOSE_{air_{scenario}} := \frac{C_{air_{scenario}} \cdot IH_{air} \cdot BIO_{inh}}{BW \cdot BIO_{oral}}$$

$$DOSE_{stem_{scenario}} := \frac{C_{leaf\_crops_{scenario}} \cdot IH_{stem}}{BW} \qquad DOSE_{root_{scenario}} := \frac{Croot_{agr\_plant_{scenario}} \cdot IH_{root}}{BW}$$

$$DOSE_{meat_{scenario}} := \frac{C_{meat_{scenario}} \cdot IH_{meat}}{BW} \qquad DOSE_{milk_{scenario}} := \frac{C_{milk_{scenario}} \cdot IH_{milk}}{BW}$$

$$DOSE_{fish_{scenario}} := \frac{C_{fish_{scenario}} \cdot IH_{fish}}{BW}$$

total daily intake for human

total daily intake for human as sum of each pathway
[$kg_{chem}*kg_{bw}^{-1}*d^{-1}$]

$$DOSE_{tot_{scenario}} := DOSE_{drw_{scenario}} + DOSE_{fish_{scenario}} + DOSE_{stem_{scenario}} + DOSE_{root_{scenario}} \ldots + DOSE_{meat_{scenario}} + DOSE_{milk_{scenario}} + DOSE_{air_{scenario}}$$

relative doses of specific different pathway (%)

$$RDOSE_{drw_{scenario}} := \frac{DOSE_{drw_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}} \qquad RDOSE_{air_{scenario}} := \frac{DOSE_{air_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}}$$

$$RDOSE_{stem_{scenario}} := \frac{DOSE_{stem_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}} \qquad RDOSE_{root_{scenario}} := \frac{DOSE_{root_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}}$$

$$RDOSE_{meat_{scenario}} := \frac{DOSE_{meat_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}} \qquad RDOSE_{milk_{scenario}} := \frac{DOSE_{milk_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}}$$

$$RDOSE_{fish_{scenario}} := \frac{DOSE_{fish_{scenario}} \cdot 100 \cdot \%}{DOSE_{tot_{scenario}}}$$

Results of calculation

$DOSE_{tot_{local}} = 7.869415 \cdot 10^{-4} \circ \frac{mg}{kg_{bw} \cdot d}$

$DOSE_{tot_{regional}} = 1.412438 \cdot 10^{-6} \circ \frac{mg}{kg_{bw} \cdot d}$

$RDOSE_{drw_{local}} = 79.875238 \cdot \%$

$RDOSE_{drw_{regional}} = 80.913788 \cdot \%$

$RDOSE_{air_{local}} = 6.665952 \circ \%$

$RDOSE_{air_{regional}} = 5.613394 \circ \%$

$RDOSE_{stem_{local}} = 11.878876 \cdot \%$

$RDOSE_{stem_{regional}} = 10.094103 \cdot \%$

$RDOSE_{root_{local}} = 0.071435 \circ \%$

$RDOSE_{root_{regional}} = 1.851155 \circ \%$

$RDOSE_{meat_{local}} = 6.981643 \cdot 10^{-4} \circ \%$

$RDOSE_{meat_{regional}} = 6.790608 \cdot 10^{-4} \circ \%$

$RDOSE_{milk_{local}} = 0.013012 \circ \%$

$RDOSE_{milk_{regional}} = 0.012656 \circ \%$

$RDOSE_{fish_{local}} = 1.494789 \circ \%$

$RDOSE_{fish_{regional}} = 1.514225 \circ \%$

European Commission

EUR 20396 EN - European Union Risk Assessment Report
Ethyl acetoacetate, Volume 13

Editors: B.G. Hansen, S.J. Munn, F. Berthault, S. Pakalin, M.Luotamo, J. de Bruijn, S. Vegro, G. Pellegrini, R. Allanou, S. Scheer.

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2002 – VIII pp., 88 pp. – 17.0 x 24.0 cm

Environment and quality of life series

The report provides the comprehensive risk assessment of the substance ethyl acetoacetate. It has been prepared by Germany in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to man and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The risk assessment for ethyl acetoacetate concludes that there is at present no concern for the environment or for human health. There is at present no need for further information and/or testing or for risk reduction measures beyond those that are being applied already.

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20396-EN-C

The mission of the JRC is to provide customer-driven scientific and technical support for the conception, development, implementation and monitoring of EU policies. As a service of the European Commission, the JRC functions as a reference centre of science and technology for the Union. Close to the policy-making process, it serves the common interest of the Member States, while being independent of special interests, private or national.

European Commission – Joint Research Centre
Institute for Health and Consumer Protection
European Chemicals Bureau (ECB)

European Union Risk Assessment Report

ethyl acetoacetate

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